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(54) 4,5,6-Substituted-2-pyrimidinamines

4,5,6-Substituierte 2-Pyrimidinamine 2-Pyrimidinamines substituées en 4,5 et 6

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Description

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BRIEF SUMMARY OF THE INVENTION

This invention relates to organic compounds and, more particularly, is concerned with 4,5,6-substituted-N-(substituted-phenyl)-2-pyrimidinamines having anti-asthmatic activity which may be represented by the following structural formula:

wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO $_2C_2H_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl-(C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfamilamido, N,N-dialkyl(C_1 - C_3)sulfamilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:

wherein R is alkyl(C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1 - C_3), alkoxy (C_1 - C_3), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1 - C_3), phenyl or morpholino and the substituents are alkyl (C_1 - C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyri-dinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1 - C_3); and R_5 is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof.

The present invention also icludes novel compositions of matter containing the above-defined compounds which are useful for treating asthma, allergic diseases, inflammation and diabetes in mammals. The invention also comprises processes of preparing the compounds within the scope of the above formula.

Non-prepublished EP-A-210 044 discloses 2-Amino-4-subst.-5-(hydroxy or alkoxy)pyrimidines useful for the treatment of pulmonary, inflammatory, allergic and cardiovascular diseases.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the present invention are obtainable as crystalline materials having characteristic melting points and absorption spectra. They are in general sparingly soluble in organic solvents such as lower alkanols, chloroform, tetrahydrofuran, N,N-dimethylformamide, dichloromethane, acetone and the like, but are generally insoluble in water.

The novel 4,5,6-substituted-2-pyrimidinamines of the present invention in general may be prepared as set forth in the following reaction schemes.

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wherein $R_1,\ R_2,\ R_3,\ R_4$ and R_5 are as hereinabove defined.

In accordance with Scheme I, a heteroaryl (R₃) alkanoyl (R₄) compound 1, e.g 2-acetylpyridine, 2-acetylfuran, 3-acetylthiophene, 2-acetyl-6-methylpyridine, 2-propionyl pyridine or 3-propionyl pyridine and the like, is reacted with a di(lower alkyl)-formamide or acetamide di(lower alkyl) acetal 2, e.g; N,N-dimethylformamide dimethylacetal or N,N-dimethylacetanide dimethylacetal at an elevated temperature in the range of about 50°C. to about 150°C for from about 4 to 24 hours to produce the 3-di(lower alkyl)aminoacrylophenone 3. The acrylophenone 3 is then reacted with an appropriately substituted phenylguanidine (R₁)(R₂), 4 as the base or as the carbonate, sulfate, nitrate, hydrochloride or dihydrochloride salt in an inert solvent such am absolute ethanol, n-propanol, isopropyl alcohol or 2-methoxyethanol and the like, by heating at the reflux temperature for from 6-48 hours. The product 5 is separated by the partial evaporation of the solvent, then cooling and collected and recrystallized in a conventional manner from solvents such as n-propyl alcohol, absolute ethyl alcohol or 2-methoxyethanol and the like and combinations of solvents such as chloroform/hexane, dichoromethane/hexane or isopropyl alcohol/ethylene glycol monomethyl ether and the like.

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Scheme II

R₅

R₁

R₂

R₄

R₃

R₃

Ethanol, Mineral HCl

Acid HN0₃

Or Dichloromethane

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wherein R₁, R₂, R₃, R₄ and R₅ are as hereinabove defind.

In accordance with Scheme II, when the 4,5,6-substituted- 2-pyrimidinamine product 5 is dissolved by heating in a solvent such as absolute ethanol, isopropyl alcohol or dichloromethane, then stirred at room temperature and reacted with a mineral acid such as sulfuric acid, hydrochloric acid, nitric acid or phosphoric acid and the like, dissolved in absolute ethanol or isopropyl alcohol and the like, the 4,5,6-substituted-2-pyrimidinamine acid addition salt 6 is precipitated on standing for 30 minutes and chilling for several hours.

Alternatively, acid addition salts may be formed with organic acidds such as citric acid or maleic acid and the like by dissolving the desired 4,5,6-substituted-2-pyrimidinamine in hot, absolute ethanol or 2-methoxyethanol in the presence of the organic acid. Cooling provides the desired compounds as solids.

The novel compounds of the present invention are highly active as antiasthmatic and antiallergic agents as will be demonstrated hereinbelow.

The bronchospasm of allergic asthma is a consequence of the release of mediators, such as histamine and slow-reacting substances from masts cells. The role of mediator release in the induction of an asthmatic attack has been fully reviewed and documented; see Kaliner, M. and Austen, K. F., Bronchial Asthma Mechanisms and Therepautics, E. B. Weiss, Editor, Little, Brown and Company, Boston, 163, (1976); Lichtenstein, L. M., Asthma-Physiology, Immunopharmacology and Treatment, Second International Symposium, L. M. Lichtenstein and K. F. Austen, Editors, Academic Press, New York, 51, (1979); and Bell, S. C., et al., Annual Reports in Medicinal Chemistry, 14, 51, H. J. Hess, Editor, Academic Press, New York, (1979).

The novel compounds of this invention have been tested by the procedure of Lichtenstein, L. M. and Osler, A. G., J. Exp. Med., 120, 507-530 (1964), which evaluates the ability of compounds to inhibit mediator (histamine) release from immunologically stimulated human basophils.

Reagents

5 10X Concentrated Tris Buffer

Dissolve 140.3 g of sodium chloride, 7.45 g of Trizma-Tris Pre-Set, Reagent Grade, pH 7.6, at 25°C (Sigma Chemical Co.) in sufficient water to give a final volume of 2 liters.

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Human Albumin

(Sigma Chemical Co.) (30 mg/ml)

5 Calcium and Magnesium Stocks

Made to 0.075 M 0.5 M respectively, with calcium chloride dihydrate and magnesium chloride hexahydrate.

Tris-A Buffer

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A 10 ml portion of 10X Tris Buffer and 1.0 ml of human albumin are diluted to 100 ml with water.

Tris ACM Buffer

A 10 ml portion of 10X Tris Buffer, 1.0 ml of human albumin, 0.8 ml of calcium stock and 0.2 ml of magnesium stock are diluted to 100 ml with water.

Rabbit Antihuman IgE

Behring Diagnostics (Generally used at 10 µg protein/ml final concentration).

House Dust Mite Extract (Dermatophagoides Farinae)

Strength 1:100 (w:v) allergenic extract, Hollister-Stier Labs. Generally this is diluted 1:1000 to 1:10,000 (considering the vial as stock).

Other Allergens

Interdermal solutions or intramuscular preparations for hyposensitization, Hollister-Steir Labs. The final concentration used is on the order of 1 PNU/ml.

Separation of Leukocytes from Human Blood and Challenge

Eighty milliliters of blood is withdrawn from subjects with known histamine release to anti-IgE, ragweed antigen or other specific allergen, using four 20 ml heparinized tubes. This 80 ml of blood is mixed with 20 ml of saline containing 0.6 g of dextrose and 1.2 g of dextran. The blood is allowed to sediment at room temperature in two 50 ml polycarbonate centrifuge tubes until a sharp interface develops between the red cells and plasma (60-90 minutes). The plasma (top) layer from each tube is withdrawn by pipet and transferred to respective 50 ml polycarbonate tubes. The plasma is centrifuged for 8 minutes at 110X G at 4°C. The supernatant is carefully poured off as completely as possible and the cell button is resuspended in 2-3 ml of Tris-A buffer using a siliconized Pasteur pipet. The resuspension is accomplished by drawing the liquid gently in an out of the pipet, with the tip below the liquid until an even suspension of cells is obtained. Sufficient Tris-A buffer is then added to bring the volume in the tube to about 45 ml and the tube is centrifuged at 110X G for 8 minutes at 4°C. The supernatant is poured off and the cell button is resuspended and centrifuged as described above. The supernatant is poured off and the cell button is suspended in 2-3 ml of Tris-ACM buffer to make the final volume sufficient to allow addition to the reaction tubes.

Reaction tubes containing anti-IgE or antigens, either alone or with test compound in a total volume of 0.2 ml are prepared and placed in a 37°C bath. The cells are warmed to 37°C and frequently swirled to ensure an even suspension, while 1.0 ml aliquots are added to each reaction tube. The tubes are then incubated for 60 minutes at 37°C, vortexing the tubes gently every 15 minutes to keep the cells evenly suspended. When the reaction is complete, the tubes are centrifuged at 4°C for 10 minutes at 1500 rpm to sediment the cells. One ml aliquots of supernatant are transferred to 12 mm by 75 mm polyethylene tubes and 0.2 ml of 8% perchloric acid is added to each tube. Blanks and totals are included in each test. The blanks have cells and all reagents except antigen or anti-IgE. The totals contain 0.24 ml of 8% perchloric acid, one ml of cells and 0.2 ml of buffer. All samples are then centrifuged to remove the precipitate protein.

Assay of Released Histamine by the Automated Fluorometric Method

This automated method has been described by Siraganian, R. P., in Anal. Biochem., <u>57</u>, 383 (1974) and J. Immunol. Methods, <u>7</u>, 283 (1975) and is based on the manual method of Shore, P. A., <u>et al.</u>, J. Pharmacol. Exp. Ther., <u>217</u>, 182 (1959).

The automated system consists of the following Technicon Autoanalyzer II components Sampler IV, Dual-Speed Proportioning Pump III, Fluoronephelometer with a narrow pass primary filter 7-60 and a secondary filter 3-74, Recorder, and Digital Printer. The manifold used is the one described by Siraganian <u>vide supra</u>, with the following modifications: the dialyzer is omitted; all pumping tubes pass through a single proportioning pump with large capacity and twice the volume of sample is taken for analysis.

The automated chemistry consists of the following steps: Extraction from alkaline saline into butanol, back extraction into dilute hydrochloric acid by addition of heptane, reaction of histamine with o-phthaldialdehyde (OPT) at high pH and conversion of the OPT adduct to a stable fluorophore with phosphoric acid. The reaction product is then passed through the fluorometer. The full scale response is adjusted to 50 ng histamine base with a threshold sensitivity of approximately 0.5 ng.

Calculation of the Results of Histamine Release Tests

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The instrument blank (wash) is substracted from the ng histamine of each sample. Then the ng histamine of each sample is divided by the mean of the three totals (cells lysed with perchloric acid) to obtain percent release.

Control samples contain antigen but no test compound. Blank (or spontaneous release) samples contain neither antigen nor test compound. The mean of the blanks (three replicates) is subtracted from the percent release for controls and test compounds.

The means for control and test compound groups are computed and the result for a test compound is computed as percent of control by the formula:

100 X % Histamine Release with Test Compound % Histamine Release in Controls

Values obtained at different concentrations of test compound are used to calculate an IC₅₀ (the concentration in µM which causes a 50% inhibition of histamine release) by linear regression. A compound is considered active if the IC₅₀ is ≤48 µM.

The results of this test on typical compounds of this invention appear in Table I.

TABLE I Inhibition of Histamine Release from Immunologically Stimulated Human Basophils

10	Compound	IC ₅₀ (µM)
	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidin-amine	17.7
15	4-(4-Pyridinyl)-N-[(3-trifluoromethyl)phenyl]-2-pyrimidinamine	32.0
20	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.4
	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine	0.9
25	N-(4-Acetylphenyl)-4-(3-pyridinyl)+2-pyrimidinamine	0.8
	N-(4-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
30	N-(4-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimi- dinamine	8.3
35	N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	1.0
	N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	1.9
40	N-(4-Bromophenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	2.3
	4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, hydrochloride	0.7
45	4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	2.9
50	N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimi- dinamine	3.9

TABLE I (continued)

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5	Compound	IC ₅₀ (µM)
10	N-(4-Ethylphenyl)-4-(1-methyl-lH-pyrrol-2-yl)-2-pyrimidinamine	<48
•	N-Phenyl-4-(2-thienyl)-2-pyrimidinamine	31.7
15	N-(3-Chloro-4-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	9.3
	N-(3-Methylphenyl)-4-(2-pyridinyl)-2-pyrimi- dinamine	0.7
20	N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	9.4
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine	0.9
25	N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	1.5
30	N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	7.7
	N-(4-Ethylphenyl)-5-methyl-4-(4-pyridinyl)-2-pyrimidinamine	<48
35	N-(4-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimi-dinamine	<48
40	N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimi- dinamine	2.1
W .	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimi-dinamine	0.3
45	4-(2-Furanyl)-N-phenyl-2-pyrimidinamine	48
	4-(2-Furany1)-N-(3-methylphenyl)-2-pyrimi-dinamine	3.5
50	N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	13.4

TABLE I (continued)

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5	Compound	IC ₅₀ (μΜ)
10	N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	19.1
	N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	<24
15	N-(4-Ethylphenyl)-4-pyrazinyl-2-pyrimidinamine	2.8
	N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimi-dinamine	5.4
20	N-(2-Methylphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	3.9
25	N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	10.6
	N-(2,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	47.1
30	N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	20.2
	N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidin-amine	3.8
35	N-(2,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	<48
40	N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	4.4
٠	N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidin-amine	31.3
45	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.0
	N-1-Naphthalenyl-4-(2-pyridinyl-2-pyrimidin-amine	3.0
50	N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	24.0
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TABLE I (continued)

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5	Compound	IC ₅₀ (µM)
10	4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	10.5
	4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidin- amine	<48
15	N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	<24
20	4-(2-Puranyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	<48
· .	N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidin- amine	13.3
25	N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine	2.2
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricar-boxylate (2:1)	3.5
30	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)	1.0
35	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	3.0
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate	1.2
40	N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidin- amine, pyridine-1-oxide	17.7
4 5	N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2- pyrimidinamine	5.9
	N-(4-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidin- amine	15.6
50	N-(3-Ethylphenyl)-4-(2-furanyl)-2-pyrimidin- amine	9.7
	4-(1 <u>H</u> -Indol-3-yl)- <u>N</u> -phenyl-2-pyrimidinamine	3.0

TABLE I (continued)

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5	Compound	IC ₅₀ (μM)
10	N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)- 2-pyrimidinamine	6.9
	N-(3-Methylphenyl)-4-(1-methyl-lH-pyrrol-2-yl)-2-pyrimidinamine	9.4
15	N-(3-Ethylphenyl)-4-(2-thienyl)-2-pyrimidin- amine	48.0
20	N-(3-Ethylphenyl)-4-(3-thienyl)-2-pyrimidin- amine	1.1
	4-(lH-Indol-2-yl)-N-(3-methylphenyl)-2-pyrimidinamine	2.2
25	4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]- benzoic acid, methyl ester	27.5
	N-(3-Methylphenyl)-4-(4-quinolinyl)-2-pyrimi- dinamine	10.9
30	N-Phenyl-4-(-4-quinolinyl)-2-pyrimidinamine	3.0
35	N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimi- dinamine	4.0
35	4-(2-Pyridiny1)-N-[3-(trifluoromethy1)pheny1]-2-pyrimidinamine, sulfate	3.0
40	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidin- arine, sulfate	3.0
	4-(2-Furanyl)-N-[3-(methylphenyl)]-2-pyrimidinamine, sulfate	3.0
45	\underline{N} -Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate	3.3
50	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimi- dinamine	0.7
	N-(3,5-Dimethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	4.3
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TABLE I (continued)

5	Compound	IC ₅₀ (µM)
10	N-(2,4-Difluorophenyl)-4-(4-pridinyl)-2-pyrimidinamine	<48
	N-(2,4-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
15	N-(3-Methylphenyl)-4-(5-methyl-2-thienyl)- 2-pyrimidinamine	1.4
20	N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	2.9
	4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	<48
25	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	<48
	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
30	4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	2.6
35	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	3.0
	N-[4-(1,1-Dimethylethyl)phenyl]-4-(3-pyridin- y 1)-2-pyrimidinamine	0.7
40	\underline{N} -(2,6-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	22.0
	N-(4-Ethylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	36.3
45	N-[(3,4-Dimethylphenyl)methyl]-4-(2-pyridinyl-2-pyrimidinamine	39.8
50	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.0.

TABLE I (continued)

5	Compound	IC ₅₀ (μM)
10	N-(3-Methylphenyl)-4-(lH-pyrrol-2-yl)-2- pyrimidinamine	11.1
	4-(5-Methyl-2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	2.0
15	4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	24.8
20	N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	3.8
20	N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	0.4
25	N-(3-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimi- dinamine	0.2
	N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	2.7
30	N-(3-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	0.3
35	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.8
-	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]- benzoic acid, ethyl ester	12.4
40	N, N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine	3.7
	4-(2,5-Dimethyl-3-furanyl)- N -phenyl-2-pyrimi-dinamine	2.0
45	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimi-dinyl)benzenediamine, trihydrochloride	0.4
50	4-(2,5-Dimethyl-3-furanyl)- \underline{N} -(3-methylphenyl)-2-pyrimidinamine	28.5
	4-(2,5-Dimethyl-3-furanyl)-N-(3,5-dimethyl-phenyl-2-pyrimidinamine	4.1

TABLE I (continued)

5	Compound	IC ₅₀ (μM)
10	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine, dihydrochloride	4.4
	4-(2,5-Dimethyl-3-furanyl)-N-(4-ethylphenyl)- -2-pyrimidinamine	19.2
15	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimi-dinyl]-1,3-benzenediamine	1.7
20	3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]ben- zoic acid, ethyl ester	3.0
	N, N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine	0.5
25	4-[[4-(3-Pyridiny1)-2-pyrimidiny1]amino]phenol	5.1
	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]ben- zoic acid, ethyl ester	20.3
30	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.2
	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	0.6
35	N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.8
40 ·	N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	2.7
45	$\underline{N}' - [4 - (2 - Furany1) - 2 - pyrimidiny1] - \underline{N}, \underline{N} - dimethyl-1, 4-benzenediamine$.1.9
	$\frac{N}{N}$, $\frac{N}{N}$ -Dimethyl- $\frac{N}{N}$ '-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzendiamine	0.6
50	N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]- $N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-$	4.9
		لـــــــــــــــــــــــــــــــــــــ

TABLE I (continued)

5	Compound	IC ₅₀ (µM)
10	N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	1.8
	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	0.3
15	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine, trihydrochloride	1.5
20	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine	3.5
	N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	37.7
25	N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
	N-[4-[2-Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.2
30	N-[4-[2-Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	0.5
35	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]ben- zoic acid	7.6
	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine, dihydrochloride	0.5
40	N, N-Dimethyl- N' -[4-(2-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine, trihydrochloride	1.0
	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-5-methyl-2-pyrimidinamine	<24
45	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine, dihydrochloride	0.5
50	N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	6.1

15

TABLE I (continued)

Compound	IC ₅₀ (µM)
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidin-amine, sulfate	5.0
<u>N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-di-</u> methyl-1,4-benzenediamine	5.6
4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimi- dinamine	26.8
4-[[4-(4-(Pyridinyl)-2-pyrimidinyl]amino]- phenol	3.3
N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	1.5
N-[4-[2-(Dimethylamino)ethoxy]phenyl]N',N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-l,2-ethanediamine	9.1
N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	1.3
N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.2
4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]- l-methylpyridinium, iodide	33.3
N.N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl)]-1,3-benzenediamine, sulfate	1.0
N, N-Dimethyl- N' -[4-(2-thienyl)-2-pyrimidinyl]- $1, 3$ -benzenediamine	2.4
N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	1.6
N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,3-benzenediamine	<24
N-[2-(Diethylamino)ethyl]-4-[[4-(3-pyridin- yl)-2-pyrimidinyl]amino]benzamide	0.8

TABLE I (continued)

5	Compound	IC ₅₀ (µM)
10	4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]- phenoxy]acetic acid, ethyl ester	5.8
	N,N-Diethyl-N'-[4-(4-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine	1.1
15	$\underline{N},\underline{N}$ -Dimethyl- \underline{N} '-[4-methyl-6-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	31.8
20	N-[4-(1H-Imidazol-l-yl)phenyl]-4-(4-pyridin-yl)-2-pyrimidinamine	12.3
	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzene-diamine, hydrochloride	3.0
25	N.N-Diethyl-N'-[4-(3-pyridinyl)-2-pyrimi- dinyl]-1,4-benzenediamine	1.7
	N-[4-(lH-Imidazol-l-yl)phenyl]-4-(3-pyridin-yl)-2-pyrimidinamine	1.3
30	l-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]- phenyl]ethanone, oxime	11.4
35	l-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]- phenyl]ethanone, O-methyloxime	5.1
	N,N-Diethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine	10.1
40	N-[4-(lH-Imidazol-l-yl)phenyl]-4-(2-pyridin-yl)-2-pyrimidinamine	1.8
	4-(2-Furanyl)-N-[4-(lH-imidazol-l-yl)phenyl]-2-pyrimidinamine	2.2
45	N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-benzamide	4.6
50	N,N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	5.7

,,,

TABLE I (continued)

5	Compound	IC ₅₀ (µM)
10	$\frac{N}{1}$, $\frac{N}{4}$ -Dimethyl- $\frac{N}{1}$ '-[4-(3-thienyl)-2-pyrimidinyl]- $\frac{N}{1}$, $\frac{N}{4}$ -benzenediamine	2.1
	N-[1-[4-[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	0.4
15	N-[4-[1-Aminoethyl)phenyl]-4-(3-pyridinyl)- Z-pyrimidinamine, trihydrochloride	0.8
	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benz- enesulfonamide	0.2
	N-(3-Chlorophenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	3.1
25	N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	1.5
	$ \frac{N}{N}$ -(3-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidin- amine	1.7
30	N-Methyl-N-[4-[[4-(3-pyridinyl)-2-pyrimidin-yl]amino]phenyl]acetamide	1.1
35	N-Methyl-N-[4-[[4-(4-pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	0.1
	N-Methyl-N-[4-[4-(2-pyridinyl)-2-pyrimidin-yl]amino]phenyl]acetamide	0.6
40	[4-(2-Furanyl)-N-(3-methoxyphenyl)-2-pyrimi-dinamine	0.3
 	4-(2-Benzofuranyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	1.2
45	Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]- amino]acetic acid, ethyl ester	2.1
50	N-[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.3

TABLE I (continued)

5	Compound	IC ₅₀ (μM)
10	N.N-Dimethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	40
	N-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	3.6
15	4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-benzenesulfonamide	4.5
	N-[4-[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	1.5
20	N-(3-Methoxyphenyl)-4-(2-thienyl)-2-pyrimi- dinamine	0.9
	N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.5
25	N-(3-Methoxyphenyl)-4-(5-methyl-2-thienyl)- 2-pyrimidinamine	2.3
30	N-(3-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.3
	4-(2-Furanyl)-N-[4-(4-methyl-1-piperazinyl)-phenyl]-2-pyrimidinamine	1.8
35	 N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(4- pyridinyl)-2-pyrimidinamine	0.6
	N-(3-Methoxyphenyl)-4-(2,5-dimethyl-3-furan- yl)-2-pyrimidinamine	5.8
40	N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzene- diamine, dihydrochloride	1.0
	N-(3-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimi- dinamine	0.7
4 5	N-(3-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	3.3
	N-(3-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.9
50	<pre>1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]- phenyl]ethanone</pre>	4.1
		<u> </u>

TABLE I (continued)

5		
·	Compound	IC ₅₀ (μΜ)
10	<u>N</u> -Methyl- <u>N</u> '-[4-(3-pyridinyl)-2-pyrimidinyl]- l,4-benzenediamine	2.1
	N-[4-(1-Methylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.1
15	\underline{N} -Methyl- \underline{N} '-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.4
	N-(3-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimi- dinamine	1.7
20	N-(3-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimi- dinamine	1.4
25	3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]ben- zenesulfonamide	0.7
	<pre>3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]ben- zenesulfonamide</pre>	0.2
30	N-[4-(1,1-Dimethylethyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	4.6
	N, N-Diethyl-N'-[4-(2-furanyl)-2-pyrimidinyl]-1,4-benzenediamine	3.4
35	3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]- benzenesulfonamide	0.5
:	N,N-Dimethyl-N'-(4-(4-pyridinyl)-2-pyrimidinyl]-1,2-benzenediamine, fumarate	36.2
40	2-[1-[4-[[4-(3-Pyridiny1)-2-pyrimidiny1]amino] phenyl]ethylidene]hydrazinecarboxamide	8.1
4 5	N-[4-[2-[bis(1,1-Dimethylethyl)amino]ethoxy]-phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	4.6
	α-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]- amino]benzenemethanol	4.5
50	N-[1-[3-[[4-(3-Pyridiny1)-2-pyrimidiny1]-amino]phenyl]ethyl]formamide	4.6
	N-[3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	2.1

. **55**

	TABLE I (continued)	
5	Compound	IC ₅₀ (μΜ)
	N-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.0
10	N-[4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	0.4
15	N, N-Diethyl- N' -[4-(5-methyl-2-furanyl)-2-pyrimidinyl]1,4-benzenediamine	28.0
	N-(3-Methoxyphenyl)-4-(5-methyl-2-furanyl)-2-pyrimidinamine	1.2
20	N-[3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.3
·	\underline{N} -[3-(1 \underline{H} -Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	0.1
25	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	1.0 .
	N-[2-Methyl-4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	1.2
30	2-Methyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	0.9
	N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzene- diamine	0.2
35	N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-amino]phenyl]acetamide	0.3
40	\underline{N} -[3-(1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	5.1
	<pre>N-[3-[2-(Diethylamino)ethoxy]phenyl*]-4-(3- pyridinyl)-2-pyrimidinamine</pre>	2.8
45	N-(2-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimi-dinamine	9.8
	N-[4-[[4-(2-Thienyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.2
50	\underline{N} -[2-Methyl-4-[4-(3-pyridinyl)-2-pyrimidinyl]-phenyl]acetamide	1.8
	N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N- diethyl-1,4-benzenediamine	. 6.2

TABLE I (continued)

_		· · · · · · · · · · · · · · · · · · ·
	Compound	IC ₅₀ (μΜ)
10	N-[4-[[4-(2-Furanyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.7
	N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.4
15	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyri- dinyl)-2-pyrimidinamine	0.1
20 ·	2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]- phenol	23.5
	4-(2-Furanyl)-N-[3-(1H-imidazol-1-yl)phenyl]- 2-pyrimidinamine	0.8
25	N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(2-furanyl)-2-pyrimidinamine	1.3
	$N-\{4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl\}-4-(2-pyridinyl)-2-pyrimidinamine$	1.6
30	N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.6
35	N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.7
	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-ben-zenediamine	2.4
40	N-[3-(lH-Imidazol-l-yl)phenyl]-4-(4-pyridinyl)- 2-pyrimidinamine	0.4
4 5	N-[3-(lH-Imidazol-l-yl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.2

The ability of these compounds to inhibit lipoxygenase activity in terms of the suppression of the release and biosynthesis of leukotriene B4(LTB4) and 5-hydroxy-eicosatetraenoic acid (5-HETE) was measured as follows.

50

In this assay $3x10^7$ peritoneal neutrophils derived from guinea pigs were incubated at 37° C in Dulbeccos buffer containing 50mM tris buffer (pH 7.4). Five minutes before the addition of 100 μ M arachidonic acid and 20 μ M calcium ionophore (A23187), control vehicle or the test compounds were added to the neutrophils at a concentration of 10 μ g/ml.

Three minutes after the addition of arachidonic acid and calcium ionophore the total lipid was partitioned into chloroform after adjusting the pH to 3 with citric acid and the addition of equal parts of methanol and chloroform.

The 5-HETE and LTB4 were resolved by HPLC using a 5 μ M 4x25 cm octadecyl silica column (IBM Instruments) with 70-80% methanol in water adjusted to pH 3.0 with acetic acid. As the mobile phase was pumped at 1.0 ml/minute, LTB4 and 5-HETE were detected by absorbance at 270 and 236 nm, respectively.

LTB4 and 5-HETE were quantitated by comparison with the control and the results were expressed as a percent of control. The lower the percentage, the more active the compound.

The results of this test on representative compounds of this invention appear in Table II.

Inhibition of Neutrophil Lipoxygenase from
Immunologically Stimulated Guinea Pig Neutrophiles

	& Int	ibit
Compound	LTB4	5- a
4-(3-Pyridinyl)-M-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	58.1	
N-(4-Acetylphenyl)-4-(3-pyridinyl)-2- pyrimidinamine		37
N-(4-Fluorophenyl)-4-(2-pyridinyl)-2- pyrimidinamine		45
M-(4-Methylphenyl)-4-(4-pyridinyl)-2- pyrimidinemine		45
R-(4-Fluorophenyl)-4-(4-pyridinyl)-2- pyrimidinamine		53
4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine		58
H-Phenyl-4-(4-pyridinyl)-2-pyrimidinam	ine	58
N-(3-Kethylphenyl)-4-(3-pyridinyl)-2- pyrimi dina mine		40
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2- pysimidinamine	33.9	41
N-(4-Ethylphenyl)-4-(2-pyridinyl)-2- pyrimidinamine	29.5	41
4-(2-Furany1)-0-(3-sethylpheny1)-2-pyr dinamine	imi- 7.4	3
N-(4-(4-Methyl-1-piperszinyl)phenyll-4- (2-thienyl)-2-pyrimidinamine	46.0	

TABLE II (continued)

5		% Inh	ibition
10	Compound	LTB4	5-HETE
	N-(4-Ethylphenyl)-4-(6-methyl-3-pyridin-yl)-2-pyrimidinamine	53.4	54.0
15	N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimi- dinamine		50.0
20	N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	36.4	28.7
	N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	58.4	
25	N-Phenyl-4-(3-thienyl)-2-pyrimidinamine		56.0
	N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimi- dinamine		48.0
30	N-(4-Ethylphenyl)-4-(3-thienyl)-2-pyrimi- dinamine		56.0
	N-(2,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine		54.0
35	N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	53.1	54.0
40	N-(2-Methoxyphenyl)-4-(4-pyridinyl)-2- pyrimidinamine	17.4	21.0
	N-(2,5-Dimethoxyphenyl)-4-(4-pyridinyl)- $\overline{2}$ -pyrimidinamine	43.2	47.0
45	N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)+2-pyrimidinamine	37.0	43.0
50	N-(2-Methoxy-5-methylphenyl)-4-(2-pyridin-yl)-2-pyrimidinamine		54.0
50		L	

25

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TABLE II (continued)

_			
5	·	% Inh	ibition
10	Compound	LTB4	5-HETE
	4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)- 2-pyrimidinamine	53.6	
15	4-(2-Furanyl)-N-(4-methoxyphenyl)-2- pyrimidinamine		44.0
20	4-(2-Furanyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	45.0	49.0
	N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimi- dinamine	33.0	
25	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)	58.0	
30	N-[(3,4-Dimethylphenyl)methyl]-4-(4-pyridinyl)-2-pyrimidinamine	24.0	36.0
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	56.0	
35	4-(2-Benzofuranyl)-N-(3-methylphenyl)-2-pyrimidinamine	46.1	·
	N-(4-Ethylphenyl)-4-(4-pyridinyl)-2- pyrimidinamine		19.0
40	N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		19.0
45	N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	17.3	35.0
	N-(4-Fluorophenyl)-4-(3-thienyl)-2-pyrimi- dinamine	51.6	
50	4-(10 <u>H</u> -Phenothiazin-2-yl)- <u>N</u> -phenyl-2- pyrimidinamine		48.0

TABLE II (continued)

5			
		% Inhibition	
10	Compound	LTB4	5-HETE
	4-(lH-Indol-3-yl)-N-phenyl-2-pyrimidin- amine	41.2	39.0
15	N-(2-Methoxy-5-methylphenyl)-4-(4-pyridin- yl)-2-pyrimidinamine	44.7	37.0
20	N-(3-Methylphenyl)-4-(1-methyl-lH-pyrrol- 2-yl)-2-pyrimidinamine		60.0
	4-(1-Methyl-lH-pyrrol-2-yl)-N-phenyl-2-pyrimidinamine		57.0
25	N-(4-Ethylphenyl)-4-(lH-indol-3-yl)-2-pyrimidinamine	56.5	
30	N-[1,1'-Biphenyl]-4-yl-(4-pyridinyl)-2-pyrimidinamine	37.1	45.0
	4-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]-benzoic acid, methyl ester	45.2	47.0
35	N-(3-Methylphenyl)-4-(4-quinolinyl)-2- pyrimidinamine	16.0	
	N-Phenyl-4-(4-quinolinyl)-2-pyrimidinamine	46.4	57.0
40 .	N-(4-Ethylphenyl)-4-(4-quinolinyl)-2- pyrimidinamine		58.0
	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	56.1	
45	N-[4-(1,1-Dimethylethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	47.8	54.0
50	N-Methyl-N-phenyl-4-(2-pyridinyl)-2- pyrimidinamine	58.1	54.0

TABLE II (continued)

5		% Inh	ibition
10	Compound	LTB4	5-HETE
	N-Phenyl-4-(lH-pyrrol-2-yl)-2-pyrimidin- amine	55.4	
15	N-(4-Ethylphenyl)-4-(lH-pyrrol-2-yl)-2-pyrimidinamine	32.6	54.0
20 .	4-(3-Pyridinyl)-N-[3-(trifluoromethyl)-phenyl]-2-pyrimidinamine sulfate	37.3	49.0
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	48.0	43.0
25	4-(3-Methyl-2-thienyl)-N-phenyl-2-pyrimi-dinamine	,	59.0
	4-(5-Methyl-2-furanyl)- N -(3-methylphenyl)-2-pyrimidinamine	59.6	
30	4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl- 2-pyrimidinamine	42.3	52.0
35	N-[4-(Dimethylamino)phenyl]-4-(4-pyridin-yl)-2-pyrimidinamine	16.6	12.4
	N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	31.2	50.0
40	N-[4-(Dimethylamino)phenyl]-4-(2-pyridin-yl)-2-pyrimidinamine	20.1	17.2
!	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	50.7	56.0
45	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	35.8	47.0
50	N,N-Dimethyl-N-'[4-(3-pyridinyl)-2-pyrimi-dinyl]-1,4-benzenediamine	43.4	34.0

TABLE II (continued)

5		% Inh	ibition
	Compound	LTB4	5-HETE
	4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	46.9	56.0
15	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydro-chloride	40.7	37.0
20	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimi-dinyl]-1,4-benzenediamine, dihydrochloride	37.6	39.0
	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenol		30.0
25	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	36.1	50.0
30	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	50.0	
	N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridin-yl)-2-pyrimidinamine	34.1	
35	N'[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dim-ethyl-1,4-benzenediamine	16.9	16.9
	N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimi-dinyl]-1,4-benzenediamine	49.8	17.8
40	N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimi-dinyl]-N,N-dimethyl-1,4-benzenediamine	21.6	17.0
4 5	$N, N-Dimethyl-N'-{4-(3-methyl-2-thienyl)-2-pyrimidinyl}-1,4-benzenediamine}$	16.4	13.6
	$N,N-D$ imethyl- $N'-\{4-(3-pyridinyl)-2-pyrimi-dinyl\}-1,4-benzenediamine, trihydrochloride$	46.8	42.0
50	N, N-Dimethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	51.1	

TABLE II (continued)

	% Inh	ibition
Compound	LTB4	5-HETE
N.N-Dimethyl-N'-[4-methyl-6-(4-pyridin- yl)-2-pyrimidinyl]-1,4-benzenediamine	1.6	10.0
N-(3,5-Dimethylphenyl)-4-methyl-6-(3-pyridinyl)-2-pyrimidinamine	32.7	40.0
$\underline{\underline{N}}' - [4-(2-\text{Furany1})-5-\text{methy1-2-pyrimidiny1}] - \underline{\underline{N}}, \underline{\underline{N}}-\text{dimethy1-1}, 4-\text{benzendiamine}$	3.6	
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimi-dinamine, sulfate	52.4	
$N' - \{4-(2-\text{Benzofuranyl})-2-\text{pyrimidinyl}\}-\underline{N}, \underline{N}-dimethyl-1, 4-benzenediamine}$	22.9	30.0
4-Methyl-N-phenyl-6-(2-pyridinyl)-2- pyrimidinamine	30.3	42.0
4-[[4-(4-Pyridiny1)-2-pyrimidiny1]-amino]-phenol		36.0
N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridin-yl-2-pyrimidinamine	57.4	
N,N-Dimethyl-N°-[4-(2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	39.6	50.0
N.N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	31.1	37.7
N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	24.1	53.6
N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	34.0	
N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]amino]phenyl]acetamide	51.0	46.0
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N, N-diethyl-1, 4-benzenediamine	51.0	45.0
N-[4-(1H-Imidazol-1-yl)-3-(trifluoro-methyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	20.0	16.0

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TABLE II (continued)

	% Inh	ibition
Compound	LTB4	5-HETE
N-[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]- 1,4-benzenediamine, dihydrochloride	47.0	28.0
Y-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyri- dinyl)-2-pyrimidinamine	50.0	51.0
<u>N</u> -[3-(1 <u>H</u> -Imidazolyl)phenyl]-4-(2-thienyl)- 2-pyrimidinamine	50.0	39.0
N-[4-(2-Furanyl)-2-pyrimidinyl]-1,4-ben- zenediamine, dihydrochloride		54.0
M-[4-(1H-Imidazol-1-yl)-3-(trifluoro-methyl)phenyl]-4-(2-pyridinyl)-2-pyrimi-dinamine		19.0
4-[[4-(2-Furanyl)-2-pyrimidinyl]amino]- benzenesulfonamide	47.0	

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The novel compounds of the present invention are effective as antiasthmatic agents in mammals when administered in amounts ranging from about 0.1 mg to about 100 mg/kg of body weight per day. A preferred dosage regimen for optimum results would be from about 0.1 mg to about 25 mg/kg of body weight per day, and such dosage units are employed that a total of from about 7 mg to about 1.8 g of the active compound for a subject of about 70 kg of body weight are administered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that these active compounds may be administered in any convenient manner such as by the oral, aerosol, intravenous, intramuscular, or subcutaneous routes.

The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets or they may be incorporated directly with the food of the diet. For oral therapeutic administration, these active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 200 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets,

pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially nontoxic in the amounts used. In addition, these active compounds may be incorporated into sustained-release preparations and formulations.

Compositions according to the present invention having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.10% to 10.0% by weight of active compound in a vehicle consisting of a polyhydric aliphatic alcohol or mixtures thereof. Especially satisfactory are glycerin, propylene glycol, and polyethylene glycols. The polyethylene glycols consist of a mixture of non-volatile, normally liquid, polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from about 200 to 1500. Although various mixtures of the aforementioned non-volatile polyethylene glycols may be employed, it is preferred to use a mixture having an average molecular weight of from about 200 to about 400.

In addition to the active compound, the parenteral solutions may also contain various preservatives which may be used to prevent bacterial and fungal contamination. The preservatives which may be used for these purposes are, for example, myristyl-gamma-picolinium chloride, benzalkonium chloride, phenethyl alcohol, p-chlorophenyl-alpha-glycerol ether, methyl and propyl parabens, and thimerosal. As a practical matter, it is also convenient to employ antioxidants. Suitable antioxidants include, for example, sodium bisulfite, sodium metabisulfite, and sodium formaldehyde sulfoxylate. Generally, from about 0.05% to about 0.2% concentrations of anti-oxidant are employed.

These compounds may also be administered by inhalation using conventional Aerosol® formulations.

The invention will be described in greater detail in conjunction with the following specific examples.

Example 1

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4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine

A 7.04 g amount of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 18.72 g of [3-(trifluoromethyl)phenyl]guanidine carbonate in 500 ml of n-propanol was heated at reflux temperature for 16 hours. The solvent was evaporated to near dryness, then water was added and the precipitate which formed was collected by filtration, then recrystallized from hexane to give 5.55 g of the desired product, mp 170-171°C.

Example 2

N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine

A mixture of 14.4 g of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one and 16.1 g of 4-methoxyphenyl guanidine carbonate in 200 ml of isopropanol was heated at reflux for 20 hours. The reaction mixture was cooled, the crude product was collected by filtration and washed with water. The material was recrystallized from isopropanol to give the desired product as light yellow crystals, mp 121-122°C.

40 Example 3

N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine

A 14.4 g amount of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 16.1 g of 4-meth-oxyphenylguanidine carbonate in 200 ml of isopropanol was heated at reflux for 24 hours. The solvent was evaporated to 1/3 volume, then the mixture was cooled in an ice-bath to crystallize the crude product. The product was collected by filtration and washed with water, then with isopropanol. The material was recrystallized from isopropanol/ethylene glycol monomethyl ether to give 16.7 g of the desired product as yellow crystals, mp 174-175°C.

Example 4

N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine

A mixture of 10.9 g of 3-dimethylamino-1-(2-thienyl)-2-propen-1-one (U. S. Patent 4,374,988) and 11.8 g of 4-meth-oxyphenylguanidine carbonate in 150 ml of isopropanol was heated at reflux for 48 hours. The solution was cooled, then filtered, giving 9.0 g of the desired product as yellow crystals, mp 158-160°C.

Example 5

4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, methyl ester

A solution of 10.0 g of 4-guanidinobenzoic acid, hydrochloride in 310 ml of methanol was mixed with 6.0 ml (9.68 g) of thionyl chloride at 0°C for 15 minutes, then stirred for one hour at room temperature and then heated at reflux for 16 hours. The solvent ws removed in yacuo and the solid was washed with ether and air dried to give 11.4 g of white crystals (A).

The above procedure was repeated using 20.0 g of 4-guanidinobenzoic acid, 11.9 ml (19.4 g) of thionyl chloride and 600 ml of methanol to give 22.6 g of white crystals (B).

The products (A) and (B) were combined and recrystallized from absolute ethanol. The product was washed with cold absolute ethanol and air dried giving 26.2 g of <u>p</u>-guanidinobenzoic acid, methyl ester, hydrochloride as white crystals, mp 137-138.5°C (dec.).

A 9.15 g amount of the above compound was partially dissolved in 100 ml of methanol (stored over 4A molecular sieves) and 2.15 g of sodium methoxide was added. The mixture was stirred briefly, then 7.0 g of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one was added and the mixture was heated under argon with stirring for 21.5 hours. The reaction mixture was cooled in an ice bath, then filtered and washed with cold methanol. The residue was dissolved in a mixture of dichloromethane and methanol and filtered to remove sodium chloride. The filtrate was concentrated on a steam bath until crystal formation. The mixture was allowed to stand at room temperature for 16 hours then was filtered. The precipitate was washed with ice cold methanol then dried and gave 5.8 g of the desired product, mp 194.5-196.5°C.

Example 6

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3-Dimethylamino-1-(3-indolyl)-2-propen-1-one

A mixture of 3.18 g of 3-acetylindole and 5.17 ml (4.36 g) of tert-butoxybis(dimethylamino)methane was heated on a steam bath for 4 hours. The cooled reaction mixture was triturated with n-hexanes and gave a semi-solid. The solvent was removed in vacuo and the material was triturated with dichloromethane giving 3.08 g of the desired compound as a tan crystalline solid, mp 239-245°C.

Example 7

3-Dimethylamino-1-(5-methyl-2-thienyl)-2-propen-1-one

A mixture of 56.08 g of 2-acetyl-5-methylthiophene and 250 ml of N.N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16 hours. The mixture was cooled in an ice bath and filtered giving 66.82 g of the desired compound, mp 118-121°C.

Example 8

3-(Dimethylamino)-1-(5-methyl-2-furanyl)-2-propen-1-one

A mixture of 37.24 g of 2-acetyl-5-methylfuran and 150 ml of N.N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16.5 hours. The solvent was removed in vacuo and the residue taken up in dichloromethane and passed through a short column of magnesium silicate. The filtrate was evaporated on a steam bath with the addition of n-hexanes to a volume of 100-150 ml. Cooling with scratching gave 28.31 g of the desired compound, mp 123-125°C.

Example 9

3-(Dimethylamino)-1-(1H-pyrrol-2-yl)-(E)-2-propen-1-one

A mixture of 39.6 g of 2-acetylpyrrole and 104 ml (87.7 g) of tert-butoxy bis(dimethylamino)methane was heated on a steam bath for 20 minutes. The reaction was allowed to subside, then heating was continued for 6 hours. The mixture solidified then was slurried in hexane with chilling. The crude product was collected, washed with hexane and dried. The solid was dissolved in chloroform containing 5% methanol and filtered through magnesium silicate. The eluent was evaporated in vacuo and the residue was recrystallized from dichloromethane/hexane containing a small amount of methanol. The solid was collected, washed with hexane then dried in vacuo giving 25.1 g of the desired compound as yellow crystals, mp 192-193°C (dec.).

The following 3-(dimethylamino)acrylophenone intermediate compounds listed in Table III were prepared in a similar manner to the procedures described in Examples 6-8 and by those described in U. S. Patents 4,281,000, 4,374,988 and in Case 29,240, Serial number 672,753, filed on November 19, 1984.

TABLE III
3-(Dimethylamino)acrylophenone Intermediates

Ex.	R ₃	R4	R ₅	MPOC	
10	2-Furanyl	H	H	84-86	
11	2-pyridinyl	Ħ	H	127-130	
12	2-furanyl	CH3	Ħ	Oil	
13	4-pyridinyl	CH3	H	106-108	
14	6-methyl-3- pyridinyl	Ħ	Ħ	116-118	
15	6-methyl-3- pyridinyl	Ħ	CH3	119-120	
16	2-pyrazinyl	Ħ	田.	132-133	
17	3-thienyl	Ħ	H	89-90	
18	4-quinolinyl	H	H		
19	3-methyl-2- thienyl	H	H	45-49	
20	l-methyl-lH- pyrrol-2-yl	H	H	94-95	
21	5-methyl-2- thienyl	Ħ	CH3	123-126	
22	2,5-dimethyl- 3-furanyl	Ħ	H	91-95	
23	2-pyridinyl	Ħ	CH ₃	68-70	

TABLE III (continued)

Ex.	R ₃	R4	R ₅	WPOC		
24	2-thienyl	н	сн3	97-99		
25	4-pyridinyl	н	CH ₃	88-89		
26	3-pyridinyl	H	СH3	62-64		
27	3-pyridinyl	СН3	H	76-78		
28	3-methyl-2- pyridinyl	Ħ	H	97-98		
29	2-benzo- furanyl	·H	H	137.0-138.5		
30	3-pyridinyl	H	H	97-99		
31	2-pheno- thiazine	H	H	·		

Examples 32-251

4.5.6-Substituted-2-pyrimidinamines

The following 4,5,6-substituted-2-pyridinamine final products listed in Table IV were obtained by reacting a 3-(dimethylamino)acrylophenone from Table III and an appropriately substituted phenylguanidine base, carbonate, sulfate, nitrate or hydrochloride salt in an inert solvent such as absolute ethanol, n-propanol, isopropanol, 2-methoxyethanol, or n-butanol and the like, with or without a base such as sodium hydroxide, potassium hydroxide or potassium carbonate and the bike by heating at the reflux temperature for from 6-90 hours, then recovering the product in a conventional

manner with recrystallization from solvents such as \underline{n} -propanol, isopropanol, absolute ethanol and the like.

ABLE IV

2-Amino-4,5,6-substituted Pyrimidinamines

MPOC	141-142	198-200	147-148	181-183	167-169	162-164	186-188
Product	Phenylguanidine carbonate 4-(2-Furanyl)-5-methyl-M-phenyl-2-pyrimidinamine	4-(4-Pyridinyl)-N-[3-(trifluoro-methyl)phenyl]-2-pyrimidinamine	Phenylguanidine carbonate N-Phenyl-4-(3-pyridinyl)-2-pyrimi- dinamine	(4-Acetylphenyl)guanidine N-(4-Acetylphenyl)-4-(3-pyridinyl)-	(4-Fluorophenyl) guanidine N-(4-Fluorophenyl)-4-(3-pyridinyl)-6-(3-pyridinyl)-6-(3-pyridinyl)-6-(3-pyridinyl)-6-(3-pyridinamine)	N(4-Methoxyphenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	(4-Fluorophenyl)guanidine N-(4-Fluorophenyl)-4-(4-pyridinyl)-carbonate
Phenylguanidine Precursor	Phenylguanidine carbonate	[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	Phenylguanidine carbonate	(4-Acetylphenyl)guanidine	(4-Fluorophenyl)guanidine carbonate	(4-Methoxyphenyl)guani- dine carbonate	(4-Fluorophenyl)guanldine carbonate
ylophenone Source	12	m ·	٦.	٦.	Ex. 1	. 11	m :
Acr	Ex.	Ä.	EX.	EX	EX	BX	Ω
EX.	32	33	34	35	36	37	38

TABLE IV (continued)

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	MPoC	174-175	176-178	161-162	137-139	140-145	135-137	157-159
	Product	N-(4-Bromophenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	(4-Fluorophenyl)quanidine N-(4-Fluorophenyl)-4-(2-thienyl)-2-carbonate	4-(2-Pyridiny1)-N-[3-(trifluoro-methy1)pheny1]-2-pyrimidinamine	Phenylguanidine carbonate N-Phenyl-4-(2-thienyl)-2-pyrimidin-amine	N-(3-Chloro-4-methylphenyl)-4-(3- pyridinyl)-2-pyrimidinamine	N-(3-Methylphenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	N-(3-Methylphenyl)-4-(4-pyridinyl)- Z-pyrimidinamine
	Phenylguanidine Precursor	(4-Bromophenyl)guanidine carbonate	(4-Pluorophenyl)quanidine carbonate	[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	Phenylguanidine carbonate	3-Chloro-4-methylphenyl- guanidine carbonate	3-Methylphenylguanidine carbonate	3-Methylphenylguanidine carbonate
	Acrylophenone Source	Ex. 1	Ex. 4	Ex. 11	Вх. 4	Ex. 1	Ex. 11	Бх. 3
į	Ex.	39	•	7	42	4 3	‡	45

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	Dodw .
46	Ex. 3	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-1-(4-pyridinyl)-2-pyrimi-	153-154
47	Ex. 1	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(3-pyridinyl)- Z-pyrimidinamine	102-103
48	Ex. 3	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(4-pyridinyl)- Z-pyrimidinamine	138-140
49	Ex. 13	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-5-methyl-4-(4- Pyridinyl)-2-pyrimidinamine	132-133
20	Ex. 3	3,4-Dichlorophenylguani-dine carbonate	N-(3,4-Dichlorophenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	214-216
- 21	Ex. 1	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(3-pyridinyl)- Z-pyrimidinamine	120-122.5
52	2 Ex. 11	4-Bthylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(2-pyridinyl)- 148.5-149.5 2-pyrimidinamine	148.5-149.5
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TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
53	BX. 4	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(2-thienyl)- Z-pyrimidinamine	112.5-114.5
54	Ex. 10	Phenylguanidine carbonate	Phenylguanidine carbonate $4-(2-Furany1)-N-phenyl-2-pyrimidin-amine$	144-145
55	Ex. 10	3-Methylphenylguanidine carbonate	4-(2-Furany1)-N-(3-methylphenyl)-2-pyrimidinamine	98-99.5
	Ex. 14	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(6-methyl-3- Pyridinyl)-2-pyrimidinamine	154-155
57	Ex. 15	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-6-methyl-4-(6- methyl-3-pyridinyl)-2-pyrimidin- amine	118-120
58	Bx. 16	4-Ethylphenylguanidine carbonate	N(4-Bthylphenyl)-4-(2-pyrazinyl)-2- pyrimidinamine	157.5-159
53	Ex. 16	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(2-pyrazinyl)- Z-pyrimidinamine	112.5-117
				•

TABLE IV (continued)

MPoC	129-130.5	126-128	131-134	121-123	104.5-105.5	139-142	183-185
Product	$\frac{N}{2}$ -Methylphenyl)-4-pyrazinyl)-2-pyrimidinamine	N-(3-Ethylphenyl)-4-(4-pyridinyl)- Z-pyrimidinamine	N-(2,5-Dimethylphenyl)-4-(4-pyri- dinyl-2-pyrimidinamine	N-(2,3-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	N-(3-Methylphenyl)-4-(3-thlenyl)- Z-pyrimidinamine	N-(2,5-Dimethylphenyl)-4-(2-pyri-dinyl)-2-pyrimidinamine	N-(3,5-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine
Phenylguanidine Precursor	2-Methylphenylguanidine carbonate	3-Ethylphenylquanidine sulfate	2,5-Dimethylphenylguani- dine carbonate	2,3-Dimethylhenylguani- dine carbonate	3-Methylphenylguanidine carbonate	2,5-Dimethylphenylguani- dine carbonate	3,5-Dimethylphenylguani- dine carbonate
Acrylophenone Source	Вх. 3	Вх. 3	Bx. 3	Bx. 3	Bx. 17	Ex. 11	Ex. 3
BX.	09	61	62	63	64	65	99

TABLE IV (continued)

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Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
67	Бх. 3	1-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(4-pyridinyl)- Z-pyrimidinamine	174-176
6.8	Ex. 11	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2- pyridinyl)-2-pyrimidinamine	114-119
69	Ex. 11	l-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(2-pyridinyl)- 2-pyrimidinamine	135-138
2	Ex. 3	2,4-Dimethylphenylguani- dine carbonate	N-(2,4-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	116-118
17	Бх. 3	2,4,6-Trimethylphenyl-guanidine carbonate	4-(4-Pyridinyl)-N-(2,4,6-trimethyl-phenyl)-2-pyrimidinamine	142-144
72	Ex. 10	4-Methoxyphenylguanidine carbonate	4-(2-Furany1)-N-(4-methoxypheny1)-2-pyrimidinamine	155-158.5
73	Ex. 10	[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	4-(2-Furanyl)-N-(3-(trifluorometh- yl)phenyl]-2-pyrimidinamine	150-154

TABLE IV (continued)

Acrylophenor Source	henone	Phenylguanidine Precursor	Product	MPOC
	Ex. 10	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(2-furanyl)- Z-pyrimidinamine	150-152
EX.	11	N-Cyclopentylguanidine sulfate	N-Cyclopentyl-4-(2-pyridinyl)-2- pyrimidinamine	106-109
Ex.	11	3,4-Dimethylphenylguani- dine carbonate	N-(3,4-Dimethylphenyl)-4-(2-pyri- dinyl)-2-pyrimidinamine	130-133.5
EX.	11	4-Methoxyphenylguanidine carbonate	N-(4-Methoxyphenyl)-4-(3-thienyl)- Z-pyrimidinamine	158-160.5
Ex.	10	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(2-furanyl)-2- Pyrimidinamine	95-98
Ex.	φ.	Phenylguanidine carbonate	Phenylguanidine carbonate $4-(1H-Indol-3-y1)-N-pheny1-2-pyrimidinamine$	188-190
Ex.	m .	2-Methoxy-5-methylphenyl- guanidine carbonate	2-Methoxy-5-methylphenyl-N-(2-Methoxy-5-methylphenyl)-4-(4-guanidine carbonate	96-98.5

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TABLE IV (continued)

BX.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoc
81	Ex. 20	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(1-methyl-lH- pyrrol-2-yl)-2-pyrimidinamine	117-120
82	Ex. 20	4-Ethylphenylquanidine carbonate	N-(4-Ethylphenyl)-4-(1-methyl-lii- pyrrol-2-yl)-2-pyrimidinamine	89-91
83	Ex. 20	Phenylguanidine carbonate	Phenylguanidine carbonate $4-(1-Methyl-lH-pyrrol-2-yl)-M-M-pyrimidinamine$	118-120
8 .	Bx. 4	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(2-thlenyl)-2- pyrimidinamine	114-116
8 2	Ex. 17	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(3-thienyl)- Z-pyrimidinamine	86-89
86	Ex. 6	3-Methylphenylguanidine carbonate	$4-(1\underline{H}-Indol-2-y1)-\underline{N}-(3-methylphen-y1)-\overline{2}-pyrimidinamine$	164-167
8.7	Ex. 18	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-quinolin- yl)-2-pyrimidinamine	196-198

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TABLE IV (continued)

MPoc	182-184	176-178	126-129	152-155	105-107	172-174	163-165
Product	Phenylguanidine carbonate N-Phenyl-4-(4-quinolinyl)-2-pyrimi-	N-(4-Ethylphenyl)-4-(4-quinolinyl)-7-pyrimidinamine	N-(3,5-Dimethylphenyl)-4-(2-fur-anyl)-2-pyrimidinamine	$\frac{N}{Y}1$)-2-pyrimidinamine	N-Methyl-N-phenyl-4-(4-pyridinyl)- Z-pyrimidinamine	N-(2,4-Difluorophenyl)-4-(4-pyrl- dinyl)-2-pyrimidinamine	N-(2,4-Difluorophenyl)-4-(3-pyri- dinyl)-2-pyrimidinamine
Phenylguanidine Precursor	Phenylguanidine carbonate	4-Ethylphenylguanidine carbonate	3,5-Dimethylphenylguani- dine hydrochloride	3,5-Dimethylphenylguani- dine hydrochloride	N-Methyl-N-phenylguani- dine hydrochloride	2,4-Difluorophenylguani- dine hydrochloride	2,4-Difluorophenylguani- dine hydrochloride
Acrylophenone Source	Ex. 18	Ex. 18	Ex. 10	Ex. 4	Ex. 3	Ex. 3	Ex. 1
Bx.	88	8	90	91	92	93	9.4

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TABLE IV (continued)

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Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
95	Ex. 7	3-Methylphenylguanídíne carbonate	N-(3-Methylphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	114-116
96	Ex. 3	2,6-Difluorophenylguani- dine hydrochloride	N-(2,6-Difluorophenyl)-4-(4-pyri-dinyl)-2-pyrimidinamine	174-176
6	Ех. 9	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-4-(1H-pyrrol-2-yl)-2-	154-157
86	Ex. 1	4-Tert-butylphenylguani- dine sulfate	N-[4-(1,1-Dimethylethyl)phenyl]-4- (3-pyridinyl)-2-pyrimidinamine	130-133
66	Бх. 1	2,6-Difluorophenylguani- dine hydrochloride	N-(2,6-Difluorophenyl)-4-(3-pyri- dinyl)-2-pyrimidinamine	163-166
3.00	Ex. 7	3,5-Dimethylhenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(5-methyl- Z-thienyl)-2-pyrimidinamine	133~135
101	Ex. 7	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	123-125

TABLE IV (continued)

Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoc
102	Ex. 11	3,4-Dimethylphenylguani- dine hydrochloride	N-[(3,4-Dimethylphenyl)methyl]-4- (2-pyridinyl)-2-pyrimidinamine	158-160
103	Ex. 7	3,5-Dimethylphenylquani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(3-methyl- Z-thienyl)-2-pyrimidinamine	151-155
104	Ex. 9	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(1H-pyrrol-2- yl)-2-pyrimidinamine	129-130
1.05	Ex. 8	3-Methylphenylguanidine carbonate	4-(5-Methyl-2-furanyl)-N-(3-meth- ylphenyl)-2-pyrimidinamine	119-121
106	Ex. 21	Phenylguanidine carbonate	Phenylguanidine carbonate 4-Methyl-6-(5-methyl-2-thlenyl)- \underline{N} - phenylguanine	133-135
107	Ex. 3	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N-[4-(Dimethylamino)phenyl]-4-(4-guanidine dihydrochloride pyridinyl)-2-pyrimidinamine	164-166
108	Ex. 3	3-Methoxyphenylguanídíne hydrochloride	N-(3-Methoxyphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	159-160
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TABLE IV (continued)

		4		8 0	2	99	18
MPOC	110-113	171-174	126-127	125-128	197-202	165-166	116-118
		<u> </u>				. -	
Product	N-(3-Methoxyphenyl)-4-(2-pyridin- yl)-2-pyrimidinamine	4-(Dimethylamino)phenyl- N-[4-(Dimethylamino)phenyl]-4-(2-guanidine dihydrochloride pyridinyl)-2-pyrimidinamine	$\frac{N-(3-Methoxyphenyl)-4-(3-pyridin-yl)-2-pyrimidinamine}{y}$	N-(3,5-Dimethylphenyl)-4-(3-pyri- dinyl)-2-pyrimidinamine	4-(Ethoxycarbonyl)phenyl- 4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-guanidine hydrochloride amino]benzoic acid, ethyl ester	N,N-Dimethyl-N'-[4-(3-pyridinyl)- 2-pyrimidinyl]-1,4-benzenediamine	Phenylguanidine carbonate 4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine
Phenylguanidine Frecursor	3-Methoxyphenylguanidine hydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride	3-Methoxyphenylguanidine hydrochloride	3,5-Dimethylphenylguani- dine hydrochloride	4-(Ethoxycarbonyl)phenyl- guanidine hydrochloride	4-(Dimethylamino)phenyl- quanidine dihydrochloride	Phenylguanidine carbonate
senone	11	11		-	-	-	22
Acrylophenone Source	Ex.	Ex. 11	Ex.	Ex.	EX.	EX.	Ex. 22
Ex.	109	110	111	112	113	114	115

TABLE IV (continued)

Acrylophenone Ex. Source 116 Ex. 17 117 Ex. 22 119 Ex. 22 119 Ex. 22			
	Phenylguanidine Precursor	Product	MPOC
	4-Ethylphenylguanidine carbonate	N-(4-Rthylphenyl)-4-(3-thlenyl)-2-pyrimidinamine	151-152.5
	3-Methylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	144-146
	3,5-Dimethylphenylguani- dine hydrochloride	4-(2,5-Dimethyl-3-furanyl)-N-(3,5-dimethylphenyl)-2-pyrimidinamine	149-152
	4-Ethylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(4-ethylphenyl)-2-pyrimidinamine	93-96
	3-Dimethylaminophenyl- guanidine dihydrochloride	3-Dimethylaminophenyl- N.N-Dimethyl-N'-[4-(3-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-I,3-benzenediamine	123-125
121 Ex. 11	3-(Ethoxycarbonyl)phenyl- guanidine hydrochloride	3-(Ethoxycarbonyl)phenyl- 3-[[4-(2-Pyridinyl)-2-pyrimidinyl]- guanidine hydrochloride amino]benzoic acid, ethyl ester	156-158
122 Ex. 11	3-(Dimethylamino)phenyl- guanidine dihydrochloride	3-(Dimethylamino)phenyl- $N, N-Dimethyl-N'-[4-(2-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-1,3-benzenediamine$	109-111

TABLE IV (continued)

MPOC	95-103	166-167	174-175	126-129	145-148	165-168	155-158
МР	95	166	174	126	14:		15
Product	3-(Ethoxycarbonyl)phenyl- 3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-guanidine hydrochloride amino]benzoic acid, ethyl ester	4-(Dimethylamino)phenyl- $\frac{N'-[4-(2-Furany1)-2-pyrimidiny1]-}{N\cdot N-dimethyl-1,4-benzenediamine}$	4-(Dimethylamino)phenyl- $\frac{N}{N}$, N-Dimethyl-N'-[4-(2-thienyl)-2-guanidine dihydrochloride pyrimidinyl]- $\frac{N}{N}$, 4-benzenediamine	4-(Dimethylamino)phenyl- N'-[4-(2,5-Dimethyl-3-furanyl)-2-guanidine dihydrochloride pyrimidinyl]-N,N-dimethyl-1,4-benzenedlamine	4-(Dimethylamino)phenyl- N.N-Dimethyl-N'-[4-(3-methyl-2-guanidine dihydrochloride thTenyl)-2-pyrimidinyl]-1,4-benzenediamine	3-(Dimethylamino)phenyl- $N.N-Dimethyl-N'-[4-(4-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-1,3-benzenediamine$	3,5-Dimethylphenylguani- $\frac{N}{2}$ (3,5-Dimethylphenyl)-4-(2-furdine
Phenylguanidine Precursor	3-(Ethoxycarbonyl)phenyl- guanidine hydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride	3-(Dimethylamino)phenyl- guanidine dihydrochloride	3,5-Dimethylphenylguani- dine
Acrylophenone Source	Ex. 1	Ex. 10	Ex. 4	Ex. 22	Ex. 19	Ex. 3	Ex. 12
EX.	123	124	125	126	127	128	129

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TABLE IV (continued)

Acrylophen Source	ن ند	enone :e	Phenylguanidine Precursor	Product	MPoc
Ex.		12	4-(Dimethylamino)phenyl- guanidine dihydrochloride	N'-[4-(2-Furanyl)-5-methyl-2- pyrimidinyl]-N'N-dimethyl-1,4- benzenediamine	146-148
Ex.		29	4-(Dimethylamino)phenyl- guanidine dihydrochloride	N'-[4-(2-Benzofuranyl)-2-pyrimi- dinyl]-N'N-dimethyl-1,4-benzene- diamine	175-178
Бх.		11	2-Guanidinobenzimidazole	N-[4-(2-Pyridinyl)-2-pyrimidinyl]- I <u>H</u> -benzimidazol-2-amine	276-279.5
Ä		23	Phenylguanidine carbonate	Phenylguanidine carbonate 4-Methyl-N-phenyl-6-(2-pyridinyl)- 2-pyrimidinamine	94-98
EX.		₹	3-(Dimethylamino)phenyl- guanidine dihydrochloride	$\frac{N}{N}$, $\frac{N}{N}$ -Dimethyl- $\frac{N}{N}$ -[4-(2-thienyl)-2- $\frac{N}{N}$	118-120
ж ж		œ	3-(Dimethylamino)phenylquanidine dihydrochloride	N,N-Dimethyl-N'-[4-(5-methyl-2- furanyl)-2-pyrimidinyl]-1,3-ben- zenediamine	126-129
Ex.		22	3-(Dimethylamino)phenyl- guanidine dihydrochloride	N'-[4-(2,5-Dimethyl-3-furanyl)-2- pyrimidinyl]-N.N-dimethyl-l,3- benzenediamine	153-155

TABLE IV (continued)

Ä.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPOC
137	Бх. 3	4-Aminoacetylphenylguani- dine hydrochloride	4-Aminoacetylphenylguani $\frac{N-[4-[[4-(4-Pyridinyl)-2-pyrimidindine]]}{yl]}$ amino]phenyl]acetamide	294-296
1.38	Ex. 3	4-(Diethylamino)phenyl- guanidine dihydrochloride	N.N-Diethyl-N'-[4-(4-pyridinyl)- Z-pyrimidinyl]-l,4-benzenedlamine	126-128
139	Ex. 1	4-(Diethylamino)phenyl- guanidine dihydrochloride	$N_{\rm M}-Diethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl)-1,4-benzenediamine$	100-104
140	Bx. 17	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-4-(3-thienyl)-2-pyrimidin- amine	142-143
141	Ex. 11	4-Pluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	207-209
142	Ex. 11	4-Chlorophenylguanidine carbonate	N-(4-Chlorophenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	220-222
143	Вх. 3	4-Methylphenylguanidine carbonate	N-(4-Methylphenyl)-4-(4-pyridinyl)- 197.5-198.5 Z-pyrimidinamine	197.5-198.5

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TABLE	2
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Bx.	Acrylophenone Source	e Phenylguanidine Precursor	Product	MPOC
144	Ex. 31	N-[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	4-(2-Phenothiazine)-N-[3-(tri- fluoromethyl)phenyl]-2-pyrimidin- amine	240-243
145	Ex. 31	4-Methoxyphenylguanidine carbonate	N-(4-Methoxyphenyl)-4-(2-pheno- thiazine)-2-pyrimidinamine	220-225
146	Бх. 31	3,4-Dichlorophenylguani- dine carbonate	N-(3,4-Dichlorophenyl)-4-(2-pheno- thiazine)-2-pyrimidinamine	235-238
147	Ex. 11	2,4-Dimethylphenylguani- dine carbonate	N-(2,4-Dimethylphenyl)-4-(2-pyri- dinyl)-2-pyrimidinamine	111.5-113.5
148	Бх. 3	2-Methoxyphenylguanidine carbonate	${ m N-(2-Methoxyphenyl)-4-(4-pyridin-Yl)-2-pyrimidinamine}$	112-117
149	Бх. 3	2,5-Dimethoxyphenylguani- dine carbonate	2,5-Dimethoxyphenylguani- N-(2,5-Dimethoxyphenyl)-4-(4-pyri-dine carbonate	151.5-155.0
150	Ex. 11	2-Methoxy-5-methylphenyl- guanidine carbonate	2-Methoxy-5-methylphenyl- N-(2-Methoxy-5-methylphenyl)-4-(2-guanidine carbonate pyridinyl)-2-pyrimidinamine	117-118.5

TABLE IV (continued)

MPOC	132-136	143-144	169-171.5	185-187	218-220	209-210	203-205
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Product	N-[(3,4-Dimethylphenyl)methyl]-4- [4-pyridinyl)-2-pyrimidinamine	4-(2-Benzofuranyl)-N-(3-methyl-phenyl)-2-pyrimidinamine	N-(3,4-Dimethylphenyl)-4-(4-pyri-dinyl)-2-pyrimidinamine	N-(4-Fluorophenyl)-4-(3-thienyl)- Z-pyrimidinamine	Phenylguanidine carbonate $4-(10H-phenothiazin-2-y1)-M-phenyl-2-pyrimidinamine$	N-(4-Ethylphenyl)-4-(1H-indol-3- yl)-2-pyrimidinamine	N-[1,1'-Biphenyl]-4-yl-4-(4-pyri- dinyl)-2-pyrimidinamine
Phenylguanidine Precursor	3,4-Dimethylphenylguani- dine hydrochloride	3-Methylphenylguanidine carbonate	3,4-Dimethylphenylguani- dine carbonate	4-Fluorophenylguanidine carbonate	Phenylguanidine carbonate	4-Ethylphenylguanidine carbonate	1,1'-Biphenylguanidine hydrochloride
Acrylophenone Source	Ex. 3	Ex. 29	Ex. 3	Ex. 17	Ex. 31	8x. 6	Ex. 3
BX.	151	152	153	154	1.55	156	157

TABLE IV (continued)

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Ex.	Acrylophenone Source	Phenylguanidine Frecursor	Product	MPoC
158	Вх. 3	[4-(1,1-Dimethylethyl)- phenyl]guanidine sulfate	N-[4-(1,1-Dimethylethyl)phenyl]- 4-(4-pyridinyl)-2-pyrimidinamine	181-183
159	Ex. 11	N-Methyl-N-phenylguani- dine hydrochloride	N-Methyl-N-phenyl-4-(2-pyridinyl)- 2-pyrimidinamine	86-91
160	Ex. 9	4-Bthylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(1 <u>H</u> -pyrrol-2- yl)-2-pyrimidinamine	131-133
191	Ex. 19	Phenylguanidine carbonate	Phenylguanidine carbonate 4-(3-Methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	137-140
162	Ex. 25	4-Dimethylaminophenyl- guanidine dihydrochloride	4-Dimethylaminophenyl- N.N-Dimethyl-N'-[4-methyl-6-(4-guanidine dihydrochloride pyridinyl)-2-pyrimidinyl)-1,4-benzenediamine	153-154
163	Ex. 26	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-methyl-6- (3-pyridinyl)-2-pyrimidinamine	136-140
164	Ex. 12	N-[3-(Trifluoromethy1)- phenyl]guanidine carbon- ate	4-(2-Furanyl)-5-methyl-N-[3-(tri- fluoromethyl)phenyl]-2-pyrimidin- amine	169-171
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TABLE IV (continued)

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Acrylophenone Ex. Source	se none		Phenylguanidine Precursor	Product	MPoc
165 Ex. 23 N-(3,5-Dimethylphenyl)-guanidine	·_	N-(3,5-Dimethyl guanidine		N-(3,5-Dimethylphenyl)-4-methyl-6- [2-pyridinyl)-2-pyrimidinamine	110-112
Ex. 10 2-Guanidinobenzimidazole	10 2-Guanidinobenzi	2-Guanidinobenzi		N-[4-(2-Furanyl)-2-pyrimidinyl]- I <u>H</u> -benzimidazol-2-amine	306.5-308
N-[4-(Dimethylamino)- phenyl]guanidine dihydro- chloride	_	N-[4-(Dimethylam phenyl]guanidine chloride	dro-	N, N-Dimethyl-N'-[4-methyl-6-(2- pyridinyl)-2-pyrimidinyl]-1,4- benzenediamine	145-148
168 Ex. 3 4-(1-Imidazolyl)phenyl-guanidine dihydrochloride	3 4-(1-Imidazolyl)pl guanidine dihydro	4-(1-Imidazolyl)pl guanidine dihydro		N-[4-(1H-Imidazol-l-yl)phenyl]-4- [4-pyridinyl)-2-pyrimidinamine	>320
169 Ex. 30 4-(1-Imidazolyl)phenyl-guanidine dihydrochloride		4-(1-Imidazolyl)p guanidine dihydro		N-[4-(1H-Imidazol-l-yl)phenyl]-4- [3-pyridinyl)-2-pyrimidinamine	134-174 (Dec.)
N-[4-Diethylamino)phen-yl]guanidine dihydro-chloride	11 N-[4-Diethylamino y1]guanidine dihy chloride	N-[4-Diethylamind yl]guanidine dihy chloride)phen-	N,N-Diethyl-N'-[4-(2-pyridinyl)-2- pyrimidinyl]-l,4-benzenediamine	138-139
Ex. 11 4-(1-Imidazoly1) guanidine dihydr	11 4-(1-Imidazolyl) guanidine dihydr	4-(1-Imidazolyl) guanidine dihydr	phenyl- ochloride	$4-(1-Imidazoly1)$ pheny1- $\frac{N-[4-(1H-Imidazo1-1-y1)]}{[2-pyridiny1)-2-pyrimidinamine}$	204-206

TABLE IV (continued)

Dodw	211-212.5	154-156	130-133	173-174	200-201	179-189 (Dec.)	120-123
Product	4-(2-Furany1)-N-[4-(1H-imidazo1-1-y1)pheny1]-2-pyrimidinamine	N.N-Dimethyl-N'-[4-(2-furanyl)-5- methyl-2-pyrimidinyl]-1,3-benzene- diamine	N.N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-1,3-ben-zenediamine	N.N-Dimethyl-N'-[4-(3-thlenyl)-2- Pyrimidinyl]-I,4-benzenediamine	N-[3-(Dimethylamino)phen- Y1]guanidine dihydro- chloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4- [2-thienyl)-2-pyrimidinamine	N-(3-Methoxyphenyl)guani- N-(3-Methoxyphenyl)-4-(3-methyl-2- dine hydrochloride thienyl)-2-pyrimidinamine
Phenylguanidine Precursor	4-(1-Imidazolyl)phenyl- guanidine dihydrochloride	N-{3-Dimethylamino)phen- Yl}guanidine dihydro- chloride	N-{3-Dimethylamino)phen- yl}guanidine dihydro- chloride	N-[4-(Dimethylamino)- phenyl]guanidine dihydro- chloride	N-[3-(Dimethylamino)phen- yl)guanidine dihydro- chloride	4-(1-Imidazolyl)phenyl- guanidine hydrochloride	N-(3-Methoxyphenyl)guani- dine hydrochloride
Acrylophenone Source	Ex. 10	Ex. 12	Ex 21	Ex. 17	Bx. 13	8x. 4	Ex. 19
Ex.	172	173	174	175	176	177	178

TABLE IV (continued)

MPOC	192-195	224-225	160-161	146-148	142-145	151-153	194-197
Product	N-[4-[4-(3-Pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]- amino]benzenesulfonamide	N-(3-Chlorophenyl)-4-(4-pyridinyl)- Z-pyrimidinamine	N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	N-(3-Methoxyphenyl)guani N-(3-Methoxyphenyl)-4-(3-thienyl) A-(3-thienyl) A-(3-th	N-(3-Methoxyphenyl)guani- N-(3-Methoxyphenyl)-4-(2-thlenyl)- Alne hydrochloride 7-pyrimidinamine	N-Methyl-N-[4-[4-(3-pyridinyl)-2- pyrim(dinyl)smino]phenyl]acetamide
Phenylguanidine Precureor	N-{4-(Acetylamino)phen- yl}guanidine hydrochlor- ide	N-(4-Benzenesulfonamido)- guanidine hydrochloride	N-(3-Chlorophenyl)guani- āine carbonate	N-(3-Chlorophenyl)guani- dine carbonate	N-(3-Methoxyphenyl)guani- dine hydrochloride	N-(3-Methoxyphenyl)guani- dine hydrochloride	[4-(acetylmethylamino)phenyl] guanidine hydrochloride
Acrylophenone Source	Ex. 30	Бх. 30	Бх. 3	Ex. 30	Ex. 17	8x. 4	Ex. 30
BX.	1.79	1 8.0	181	182	183	184	185

TABLE IV (continued)

Β×.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPOC
186	Бх. 3	[4-(acetylmethylamino)phenyl] -guanidine hydrochloride	[4-(acetylmethylamino)phenyl] N-Methyl-N-[4-[[4-pyridinyl]-2- % - quanidine hydrochloride pyrimidinyl]amino]phenyl]acetamide	233-234
167	Ex. 11	<pre>[4-(acetylmethylamino)phenyl] -guanidine hydrochloride</pre>	[4-(acetylmethylamino)phenyl] N-Methyl-N-[4-[[4-(2-pyridinyl)-2-guanidine hydrochloride pyrimidinyl]amino]phenyl]acetamide	179-181
188	Ex. 10	N-(3-Methoxyphenyl)guani- dine hydrochloride	N-(3-Methoxyphenyl)guani- 4-(2-Furanyl)-N-(3-methoxyphenyl)- 3-fine hydrochloride	114-116
189	Ек. 29	N-(3-Methoxyphenyl)guani- dine hydrochloride	N-(3-Methoxyphenyl)guani- 4-(2-Benzofuranyl)-N-(3-methoxy- dine hydrochloride phenyl)-2-pyrimidinamine	137
190	8 . x3	N-(Ethylphenyl)guanidine carbonate	N-(4-Ethylphenyl)-4-(1-methyl-1 <u>11</u> - pyrrol-2-yl)-2-pyrimidinamine	89-91
161	Ex. 3	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(4-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]acetamide	294-296
192	Ex. 10	N,N-Dimethylphenylguani- dine dihydrochloride	N.N-Dimethyl-N'-{4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzene-diamine	154-156

TABLE IV (continued)

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Acryl Sc	ylophe Source	Acrylophenone Source	Phenylguanidine Frecursor	Product	MPOC
	Ех. 30	91	N-Acetylphenylguanidine Nydrochloride	N-[4-[[4-(3-Pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	192-195
	Ex. 1	-	Sulfonylaminophenyl- guanidine hydrochloride	4-[[4-(2-Pyridinyl)-2-pyrimidinyl]-amino]benzenesulfonamide	274-277
	Ex. 1		N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(2-Pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	254-255
	Ex. 4		3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-thienyl)- Z-pyrimidinamine	151-153
	Вх. 3	30	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(3-pyridinyl)-2-pyrimi- dinamine	174-175
	Ex. 7		3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	149-151
	Ex. 1	11	3-Chlorophenylguanidine hydrochloride	N-(3-Chlorophenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	164-165

TABLE IV (continued)

×	Acrylophenone Ex. Source	none	Phenylguanidine Precursor	Product	MPOC
200	Bx. 10	0	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	$4-(2-Furany1)-\underline{N}-[4-(4-methy1-1-piperaziny1)pheny1]-2-pyrimidin-amine$	193-195
201	Ex. 4	,	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(2-thienyl)-2-pyrimidin- amine	215.5-216.5
202	Ex. 1]	-4	4-(4-Methylpiperazin-l- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(2-pyridinyl)-2-pyrimi- dinamine	192-193

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TABLE IV (continued)

EX.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
203	Ex. 13	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-1-piperazinyl)- phenyl]-4-(4-pyridinyl)-2- pyrimidinamine	207-209
204	Ex. 22	<pre>J-Methoxyphenylguani- dine hydrochloride</pre>	N-(3-Methoxyphenyl)-4-(2,5-dimeth- yl-3-furanyl)-2-pyrimidinamine	124-125
205	Ex. 13	3-Fluorophenylguani- dine hydrochloride	N-(3-Fluorophenyl)-4-(4-pyridinyl)- 2-pyrimidinamine	162
206	Ex. 30	1-Fluorophenylguani- dine hydrochloride	N-(3-Fluorophenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	147-150
207	Ex. 11	<pre>1-Fluorophenylguani- dine hydrochloride</pre>	N-(3-Fluorophenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	162-164
208	פר .א?	4-Acctylphonylguani- dine	1-{3-{4-(3-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]ethanone	166-168
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TABLE IV (continued)

<u>α</u>	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
209	Ех. 30	1-(Methylethyl)phenyl- guanidine hydrochloride	N-[4-(1-Methylethyl)phenyl)-4-(3- pyridinyl)-2-pyrimidinamino	124-125
210	Ex. 30	<pre>1-Ethylphenylguanidine hydrochloride</pre>	N-(3-Ethylphenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	80-88
211	Ex. 11	1-Ethylphenylguanidine hydrochloride	N-(3-Ethylphenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	101-104
212	Ex. 11	3-Benzenesulfonamido- guanidine hydrochloride	<pre>3-[[4-(2-Pyridinyl)-2-pyrimidinyl]- amino]benzenesulfonamide</pre>	223-225
213	Ех. 30	J-Benzenesulfonamido- guanidine hydrochloride	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]- amino]benzenesulfonamide	278-280
714	Ex. 24	4-(1,1-Dimethylethyl)- phenylguanidine hydro- chlorido	N-[4-(1,1-Dimethylethyl)phenyl]-4- [2-thienyl)-2-pyrimidinamine	150-154
215	Ex. 10	4-(Diethylamino)phenyl- guanidine hydrochloride	N,N-Diethyl-N'-(4-(2-furanyl)-2- pyrimidinyl]-1,4-benzenediamine	132-133

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
216	Ex. 13	4-Benzenesulfonamido- guanidine hydrochloride	3-[[4-(4-Pyridinyl)-2-pyrimidinyl]- amino]benzenesulfonamide	262-264
217	Ex. 13	4-Acetylaminophenyl- guanidine hydrochloride	N-[3-[(4-(4-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]acetamide	267-270
218	Ex. 30	4-Acetylaminophenyl- guanidine hydrochloride	N-[3-[[4-(3-Pyridinyl)-2-pyrimi- dinyl]amino]phonyl]acetamide	239-241
219	Ex. 11	<pre>3-Acetylaminophenyl- guanidine hydrochloride</pre>	N-[3-[4-(2-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]acetamide	190-192
220	Ex. 13	3-(1H-Imidazol-1-yl)- phenylguanidine di- hydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4- (4-pyridinyl)-2-pyrimidinamine	232-234
221	Ex. 13	4-Acetylamino-3-methyl- phenylguanidine hydro- chloride	N-[2-Methyl-4-[[4-(4-pyridinyl)-2- pyrimidinyl]amino]phenyl]acetamide	230-235
222	Ex. 21	4-Acetylaminophenyl- guanidine hydrochloride	N-[4-[[4-(5-Methyl-2-thienyl)-2- pyrimidinyl]amino]phenyl]acetamide	227-230

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TABLE IV (continued)

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MP ^O C	79-82	99-101	201-203	233-235	134-136	230-232
Product	N-[3-[2-(Diethylamino)ethoxy]phen- yl]-4-(3-pyridinyl)-2-pyrimi- dinamine	N-(2-Methoxyphenyl)-4-(3-pyridin- yl)-2-pyrimidinamine	N-[4-[[4-(2-Thienyl)-2-pyrimidin- yl]amino]phenyl]acetamide	N-{2-Methyl-4-{4-(3-pyridinyl)-2- pyrimidinyl]phenyl]acetamide	N'-[4-(2-Benzofuranyl)-2-pyrimidin- yl]- <u>N,N</u> -diethyl-1,4-benzenediamine	N-[4-[[4-(2-Furanyl)-2-pyrimidin- yl]amino]phenyl]acetamide
Phenylguanidine Precursor	<pre>3-(2-(Diethylaminoeth- oxy)phenyl]guanidine dihydrochloride</pre>	2-Methoxyphenylguan1- dine carbonate	4-Acetylaminophenyl- guanidine hydrochloride	4-Acetylamino-3-methyl- phenylguanidine hydro- chloride	4-Diethylaminophenyl- guanidino hydrochlorido	4-Acetylaminophenyl- guanidine hydrochloride
Acrylophenone Source	Ex. 30	Ex. 30	Ex. 24	Ex. 10	Ex. 29	Ex. 12
Ex.	223	224	225	226	227	228

TABLE IV (continued)

EX.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
229	Ex. 13	4-(Imidazol-1-yl)-3- (trifluoromethyl)phen- ylguanidine dihydro- chloride	N-[4-(lll-Imidazol-1-yl)-3-(tri- fluoromethyl)phenyl]-4-(4-pyridin- yl)-2-pyrimidinamine	238-239
230	Ex. 11	4-Acetylamino-J-methyl- phonylguanidine hydro- chloride	N-[2-Methyl-4-[[4-(2-pyridinyl)-2- pyrimidinyl]amino]phonyl]acotamide	232-234
231	Ex. 30	<pre>3-(1-Imidazolyl)phenyl- guanidine dihydro- chloride</pre>	N-(3-(1H-Imidazol-1-yl)phenyl)-4- (3-pyridinyl)-2-pyrimidinamine	137-144
232	Ex. 24	<pre>3-(1-Imidazolyl)phenyl- guanidine dihydro- chloride</pre>	N-(3-(111-Imidazoly1)phenyl]-4-(2- thienyl]-2-pyrimidinamine	183-184.5
233	Fx. 10	<pre>3-(1-Imidazolyl)phenyl- guanidine dihydro- chloride</pre>	4-(2-Furanyl)-N-(3-(111-imidazol-1- yl)phenyl]-2-pyrimidinamine	160-168

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Ω×	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
234	Ex. 10	<pre>1-(Diethylamino)ethoxy- phenylguenidine dihydro- chloride</pre>	<pre>3-(Diethylamino)ethoxy- N-(3-{2-(Diethylamino)ethoxy)phen- phenylguenidine dihydro- y1]-4-(2-furanyl)-2-pyrimidinamine chloride</pre>	
235	Ex. 10	3-Methylphenylguanidine hydrochloride	4-(2-Furanyl)-N-(3-methylphenyl)-2- pyrimidinamine, hydrochloride	195-199
236	Ex. 11	4-(1-Imidazolyl)-3-(tri- fluoromethyl)phenyl- guanidine dihydro- chloride	4-(1-Imidazolyl)-3-(tri- N-[4-(111-Imidazol-1-yl)-3-(tri- fluoromethyl)phenyl- guanidine dihydro- yl)-2-pyrimidinamine	216-218
237	Ex. 24	<pre>3-(Diethylamino) ethoxy- phenylguanidine di- hydrochloride</pre>	N-[3-(2-(Diethylamino)ethoxy)phen- yl]-4-(2-thienyl)-2-pyrimidinamine	
238	Ex. 10	4-Benzenesulfonamido- guanidine hydrochloride	4-{[4-(2-Furanyl)-2-pyrimldinyl]- amino}benzenesulfonamide	255-257
239	Ex. 21	4-Benzenesulfonamido- guanidine hydrochloride	4-[[4-(5-Methyl-2-thlonyl]-2- pyrimidinyl]amino]benzenesul- fonamide	241-245

TABLE IV (continued).

Ex.	Acry lophenone Source	Phenylguanidine Precursor	Product	МР ^О С
240	Ex. 17	[4-(acetylmethylamino) phenyl]-guanidine hydrochloride	N-Methyl-N-[4-([4-(3-thienyl)-2- pyrimidinyl]amino]phenyl]acetamide	150-153
241	Ех. 13	3-[4-Methyl-1-pipera- zinyl]phenylguanidine hydrochloride	N-[3-(4-Methyl-1-piperazinyl)phen- yl]-4-(4-pyridinyl)-2-pyrimidina- mine	150-151.5
242	Ex. 10	<pre>3-[4-Methyl-l-pipera- zinyl)phenylguanidine hydrochloride</pre>	4-(2-Furanyl)-N-[3-(4-methyl-1- piporazinyl)phenyl]-2-pyrimidina- mine	134.5-136
243	Ex. 24	<pre>3-[4-Methyl-1-pipera- zinyl]phenylguanidine hydrochloride</pre>	N-[3-(4-Methyl-1-piperazinyl)phen- yl]-4-(2-thienyl)-2-pyrimidinamine	125-126.5
244	Ex. 13	2-Dimethylaminophenyl- guanidine dihydro- chloride	N, N-Dimethyl-N'-(4-(4-pyridinyl)-2-pyrimidinyl)-2-pyrimidinyl]-l,2-benzenediamine	114-119

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TABLE IV (continued)

٧	Acrylophenone Source	Phenylguanidine Precursor	Product	мР ^о с
ω 	бх. 13	<pre>3-(Diethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-[3-[2-(Diethylamino)ethoxy]phen- yl]-4-(4-pyridinyl)-2-pyrimidina- mine	100-103
	Ex. 24	<pre>3-(Diethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-{4-{2-(Diethylamino)ethoxy]phen- yl]-4-(2-thienyl)-2-pyrimidinamine	
	Ex. 24	<pre>3-(Dimethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	3-(Dimethylamino)ethoxy- N-[4-[2-(Dimethylamino)ethoxy]phen-phenylguanidine di- y1]-4-(2-thienyl)-2-pyrimidinamine hydrochloride	96-98
	Ех. 17	<pre>3-(Dimethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	3-(Dimethylamino)ethoxy- $N-\{4-\{2-\{Dimethylamino\}ethoxy\}phen-phenylguanidine di-yl]-4-(3-thienyl)-2-pyrimidinamine hydrochloride$	83-85
	Ex. 21	4-Diethylaminophenyl- guanidine hydrochloride	N,N-Diethyl-N'-[4-(5-methyl-2-fur- anyl)-2-pyrimidinyl]-1,4-benzene- diamine	118-119
	Ex. 21	3-Methoxyphenylguani- dine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2- furanyl)-2-pyrimidinamine	
	Ex. 13	3-(1H-Imidu zol-1-y 1)- phenylguanidine di- hydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4- -(4-pyridinyl)-2-pyrimidinamine	232-239

Example 252

1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone, oxime

A 2.03 mg portion of N-(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was mixed with 210 ml of absolute ethanol and 1.26 g of hydroxylamine hydrochloride. An 18.2 ml portion of 1N sodium hydroxide was added, the mixture was heated at reflux for 2 hours and then evaporated to 1/4 volume. This was cooled, the solid collected, washed with ethanol and water and dried, giving 1.9 g of the desired product as cream colored crystals, mp 239-241°C.

10 Example 253

1-[4-[[4-(3-Pyridinyl]-2-pyrimidinyl]amino]phenyl]ethanone.O-methyloxime

The procedure of Example 252 was repeated using methoxyamine hydrochloride, giving 1.78 g of the desired product as yellow crystals, mp 163-167°C.

Example 254

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N-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethyl]formamide

A mixture of 7.25 g of N-(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, 100 ml of formamide and 31 ml of 98% formic acid was refluxed with stirring overnight. The solvents were then boiled off for 1/2 hour, the reaction cooled and poured into one liter of water. This was extracted with 725 ml of chloroform. The chloroform extract was back washed with 150 ml of water, then dried, filtered and evaporated to a foam. The foam was partitioned between chloroform and water. An equal volume of saturated potassium bicarbonate was added. The organic phase was separated, dried, filtered and evaporated to a foam. This foam was chromatographed on silica gel topped with a thin layer of hydrous magnesium silicate and eluted with chloroform (first four fractions), then with 2% methanol in chloroform (last two fractions). The sixth (final) fraction was evaporated and then crystallized from chloroform-hexane, giving 1.05 g of the desired product as cream colored crystals, mp 118-121°C.

Example 255

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 1.10 g portion of dry 4-[[4(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 25 ml of dimethylformamide. A 213 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A 480 mg portion of 2-dimethylaminoethyl chloride in 2 ml of dimethylformamide was added and the sealed mixture was stirred overnight. The solvent was removed at 60°C and the residue partitioned between 25 ml of water and 50 ml of ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The organic phases were combined, washed with 1N sodium hydroxide, dried, filtered and evaporated. The residue was taken up in 20 ml of chloroform, boiled down to 1/3 volume and hexane added to turbidity. The mixture was allowed to stand overnight, giving 400 mg of the desired product as beige crystals, mp 108-110°C.

Example 256

N-[4-[3-(Dimethylamino)propoxylphenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 5.46 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with 3-dimethylaminopropyl chloride by the procedure of Example 255, giving 2.9 g of the desired product, mp 85-87°C.

Example 257

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 256 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 300 mg of the desired product as yellow crystals, mp 85-87°C.

Example 258

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

The procedured of Example 255 was repeated, using 2-diethylaminoethyl chloride, giving 3.45 g of the desired product as yellow crystals, mp 87-89°C.

Example 259

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 255 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 1.6 g of the desired product as yellow crystals, mp 120-122°C.

15 Example 260

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-N', N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1, 2-ethanediamine

The procedure of Example 259 was repeated. Subsequent crops of crystals gave 0.4 g of the desired product, mp 20 87-91°C.

Example 261

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N-[4-[3-(Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

A 2.78 g portion of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol and 2.35 g of 3-dimethylaminopropyl chloride were reacted as described in Example 255, giving 850 mg of the desired product, mp 123-124.5°C.

Example 262

[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid, ethyl ester

A mixture of 5.58 g of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with ethyl bromo acetate as described in Example 255, giving 1.8 g of the desired product as yellow crystals, mp 109-111°C.

Example 263

N-(4-Methoxyphenyl)-N-methyl-4-(3-pyridinyl)-2-pyrimidinamine

40 A 2.78 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 30 ml of dimethylformamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction sealed and stirred for 45 minutes. A solution of 1.70 g of methyl iodide in 2 ml of dimethylformamide was added, the sealed mixture was stirred overnight and the solvent removed. The residue was partitioned between water and chloroform. The organic phase was dried, filtered and evaporated. The residue was crystallized from ether-hexane giving 1.4 g of the desired product as yellow crystals, mp 88-90°C.

Example 264

N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 263 was repeated using \underline{N} -(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 510 mg of the desired product as yellow crystals, mp 124-126°C.

Example 265

N-[2-(Diethylamino)ethyl]-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide

A 1.55 ml portion of diethylethylenediamine was added to a solution of 0.01 mole of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid chloride in 50 ml of 1,2-dimethoxyethane. A 10 ml portion of triethylamine was added and the

mixture was stirred for 2 hours. The solid was collected, washed with water and recrystallized from absolute ethanol, giving 1.22 g of the desired product, mp 148-150°C.

Example 266

N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide.

A 5.85 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid in 30 ml of thionyl chloride was refluxed on a steam bath for one hour, then evaporated to dryness. The residue was boiled with dimethoxyethane, then cooled and the solid recovered and washed with ether, giving 6.90 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid chloride.

A 6.03 g portion of the above acid chloride was suspended in 25 ml of ethanol and 10 ml of 25% aqueous methyl amine was added. The resulting solid was collected, taken up in hot 2-methoxyethanol, cooled and the solid collected, giving 3.35 g of the desired product, mp 254-257°C.

15 Example 267

4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid

To a solution of 19.89 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester in 200 ml of 3A ethanol was added 12.5 ml of 10N sodium hydroxide. This mixture was refluxed on a steam bath for 3 hours and then allowed to evaporate. The residue was taken up in water and treated with 10.4 ml of concentrated hydrochloric acid. The resulting solid was collected and dried, giving 18.11 g of the desired product, mp 311-317°C.

Example 268

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[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid

An 800 mg portion of [4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid, ethyl ester was dissolved in 100 ml of ethanol and 10.7 ml of 1N sodium hydroxide was added. The mixture was stirred for 2 hours, the solvent removed and the residue dissolved in 5 ml of water. The pH was adjusted to 7.0 with 1N hydroxhloric acid and the solid collected, washed with water and dried. The solid was recrystallized from dimethylformamideethanol, giving 600 mg of the desired product as yellow crystals, mp 308-310°C.

Example 269

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4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium iodide

A 2.0 g portion of N-(4-methoxyphenyl)-4-(4-pyridinyl-2-pyrimidinamine was dissolved in 550 ml of absolute ethanol and filtered. To this was added 10 ml of iodomethane. The reaction was heated on a steam bath for 4 hours. Another 10 ml of iodomethane was added and refluxing was continued overnight. The mixture was cooled, the solid collected, washed with ethanol and dried, giving 2.2 g of the desired product as purple crystals, mp 282-284°C.

Example 270

45 4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

A 25.0 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 200 ml of 48% hydrobromic acid and stirred overnight under an argon atmosphere. The mixture was then heated on a steam bath for 7 hours, cooled overnight and evaporated at 60°C. The residue was basified with 200 ml of saturated potassium bicarbonate solution and stirred for 1.5 hours. The solid was collected, washed with water, dried and recrystallized from hot absolute ethanol, giving 19.1 g of the desired product, mp 223-225°C.

Example 271

55 4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenol

The procedure of Example 270 was repeated using \underline{N} -(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 3.0 g of the desired product as yellow crystals, mp 268-270°C.

Example 272

N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 2.73 g portion of dry 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 50 ml of dry dimethylformamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A solution of 1.33 g of allyl bromide in 10 ml of dimethylformamide was added, the sealed mixture was stirred overnight and then evaporated at 80°C. The residue was partitioned between water and chloroform. The organic phase was separated, dried and filtered. The filtrate was evaporated and the residue crystallized from chloroform-hexane, giving 1.7 g of the desired product as yellow crystals, mp 105-108°C.

Example 273

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N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, pyridine-1-oxide

A mixture of 2.76 g of N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine and 3.45 g of m-chloroperbenzoic acid in 100 ml of dichloromethane was stirred at room temperature for 20 hours. The mixture was washed three times with an aqueous saturated solution of sodium bicarbonate and a small amount of saturated saline. The organic layer was dried over magnesium sulfate, filtered through diatomaceous earth, then evaporated in vacuo to give a gelatenous solid. The solid was slurried with 50 ml of dichloromethane and filtered. The solid was washed with a small amount of dichloromethane and air dried to give 500 mg of the product. Recrystallization from absolute methanol gave 460 mg of the desired product, mp 223-225°C.

Example 274

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 70 ml of dichloromethane with warming. The solution was cooled to room temperature, then hydrogen chloride gas was bubbled in to give a brick red precipitate. The mixture became very thick and more dichloromethane was added. The precipitate was collected, air dried, then dried in vacuo and gave 2.63 g of the desired product as red-orange crystals, mp 259-262°C.

Example 275

N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1.4-benzenediamine. hydrochloride

A 2.85 g amount of N-[4-[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide was added to a mixture of 10 ml of concentrated hydrochloric acid and 10 ml of water. The reaction mixture was heated at reflux for 90 minutes, then evaporated in vacuo to obtain a solid. The solid was recrystallized from 3A ethanol/water and gave 2.31 g of the desired product as a yellow crystalline solid, mp 292-295°C.

Additional hydrochloride salts listed in Examples 276 to 287 in Table V were obtained from the corresponding base compound by following procedures similar to those described in Examples 274 and 275 and employing various other

solvents such as isopropyl alcohol, ethanol, ether and the like.

TABLE V

	Ex	Compound	MP°C
5	276	4-(3-Pyridinyl)-N-[3-trifluoromethyl)phenyl]pyrimidinamine, hydrochloride	220-223
	277	N.N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	239-245
	278	N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	115-150 (dec)
10	279	N.N-Dimethyl-N'-[4-(2-pyridinyl)-2-(pyrimidinyl)]-1,3-benzenediamine, dihydrochloride	204-213
	280	N.N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, trihydrochloride	202-205
	281	N.N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	178-184
	282	N-N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	229-234
15	283	N.N-Dimethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	232-235
	284	N-[4-(1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	
	285	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine, hydrochloride	232.5-234
20	286	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine, hydrochloride	259-266
	287	4-(2-Furanyl)-N-[3-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine, hydrochloride	259-263

Example 288

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N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine. sulfate

A 2.48 g amount of $\underline{\text{N}}$ -phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 120 ml of absolute ethanol with heating, then a solution of 1.02 g of concentrated sulfuric acid in 25 ml of ethanol was added dropwise with stirring. The mixture turned orange then a yellow precipitate formed. The mixture was chilled, the precipitate was collected, by filtration, washed with cold ethanol then with ether, and air dried to give 2.73 g of yellow-orange crystals.

The preceding compound was dissolved in a small amount of water, then a saturated aqueous solution of sodium bicarbonate was added to pH 8.0 to yield a light yellow precipitate. The precipitate was collected, washed with water and dried in vacuo. A 2.25 g portion this material was recrystallized from about 200 ml of absolute methanol in the cold. The product was collected, washed with absolute ethanol and dried in vacuo to give 1.75 g of the desired product as orange cyrstals, mp 233-235°C.

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Additional sulfate salts which were prepared from the corresponding base compound in the manner described here-inabove are listed as Examples 289 to 300 in Table VI.

TABLE VI

Ex	Compound	MP°C
289	4-(2-Pyridinyl)-N-[3-trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	208-211
290	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine, sulfate	207.5-210
291	4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine sulfate	187-193
292	4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl)]-2-pyrimidinamine, sulfate	250-253
293	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	103-123
294	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	167-187
295	4-(3-Pyridinyl)-N-[3-trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	196-199
296	N-(3,5-Dimethylphenyl)-[4-(3-pyridinyl)-2-pyrimidinamine, sulfate	209-214
297	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	216-218
298	N-(3,5-Dimethylphenyl)-4-methyl-6-(5-methyl-2-thienyl)-2-pyrimidinamine, sulfate	232-234
299	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	140-144
300	N.N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, sulfate	204-211

Example 301

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N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 2.07 g of phosphoric acid in 25 ml of ethanol was added with stirring. The mixture was chilled for several hours, then the precipitate which formed was collected by filtration, washed twice with cold ethanol and dried in vacuo for 16 hours to give 3.43 g of the desired product as orange crystals, mp 210.5-212.5°C.

Additional phosphate salts which were prepared from the corresponding base compound in the manner described hereinabove are listed as Examples 302 to 305 in Table VII.

TABLE VII

Ex	Compound	MP°C
302	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	190-192
303	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	185-188
304	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine phosphate	176-179
305	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	199-202

Example 306

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)

A mixture of 4.97 g of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 2.55 g of maleic acid was dissolved in hot 2-methoxyethanol. Cooling gave 4.15 g of the desired product as an orange crystalline solid, mp 211-214°C.

Example 307

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 1.5 ml of concentrated nitric acid in 25 ml of ethanol was added with stirring to give a red-orange precipitate. The mixture was allowed to stand 30 minutes at room temperature, then was chilled for several hours. The solid was collected, washed with cold absolute ethanol and air dried to give 2.80 g of the desired product as red-orange crystals, mp 167-169°C (dec.).

Example 308

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N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

A mixture of 4.97 g of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 4.62 g of citric acid was dissolved in hot absolute ethanol. Cooling gave 6.14 g of the product of the example as a yellow cystalline solid, mp 155-157°C.

Example 309

Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]amino]acetic acid, ethyl ester

A 4.08 g portion of 2-phenylamino-4-(4-pyridinyl)pyrimidine was dissolved in 20 ml of dimethylformamide. A 5 g portion of 50% sodium hydride in oil was added using 10 ml of dimethylformamide as a wash. When bubbling ceased, a solution of 2.23 ml of ethyl oxalyl chloride in 10 ml of dimethylformamide was added dropwise. Chloroformand aqueous 10% potassium bicarbonate were added. The organic layer was separated, dried, filtered and evaporated giving the desired product.

Example 310

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride

A 12.86 g portion of N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide in a mixture of 40 ml of water and 40 ml of concentrated hydrochloric acid was refluxed for 30 minutes and then cooled. The solid was collected and dried, giving 10.84 g of the desired product, mp 285-288°C.

Following the procedure of this Example, and using as starting materials the products of the indicated examples, the products or Examples 311-322 in Table VIII were derived.

TABLE VIII

5	Ex.	Starting Material	Product	MP°C
	311	Ex. 185	N-Methyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	164-166
	312	Ex. 187	N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	110-112
10	313	Ex. 218	N-[4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	279-284
10	314	Ex. 217	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	199-202
	315	Ex. 221	$\hbox{$2$-Methyl-$\underline{N}_{-}$ [4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, $$ dihydrochloride $$$	297-304
15	316	Ex. 219	\underline{N} -[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	153-156
	317	Ex. 182	N-[3-(1-Aminomethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	230(dec.)
	318	Ex. 222	$\underline{\text{N}}\text{-}[4\text{-}(5\text{-Methyl-}2\text{-thienyl})\text{-}2\text{-pyrimidinyl}]\text{-}1,4\text{-benzenediamine}, dihydrochloride}$	284-287
20	319	Ex. 228	N-[4-(2-Furanyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	261-266
•	320	Ex. 226	2-Methyl-N-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	176-178
	321	Ex. 230	2-Methyl-N-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	196-198
25	322	Ex. 191	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	192-193.5

Example 323

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2-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethylidene]hydrazinecarboxamide

A 2.9 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was mixed with 1.23 g of semicarbazide hydrochloride in 200 ml of absolute ethanol and 1.10 ml of 10N sodium hydroxide was added. This mixture was refluxed overnight, then cooled to room temperature and the solid collected and washed with ethanol, water and ethanol. The solid was recrystallized from dimethylsulfoxide/ethanol, giving 2.9 g of the desired product, mp 256-258°C.

Example 324

N-[4-[2-[bis(1-Methylethyl)amino]ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 2.64 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 60 ml of dimethylformamide by warming on a steam bath and then cooled. A 2.0 g portion of diisopropylaminoethyl chloride hydrochloride was added and dissolved with stirring. A 20 ml portion of 5N sodium hydroxide was added dropwise over 5 minutes, then 5 ml of water was added and the mixture was stirred for 20 hours. The mixture was then heated on a steam bath for 30 minutes, allowed to stand 48 hours and then evaporated. The residual gum was purified by flash dry column chromatography on silica gel eluting fractions 1-3 with methanol and fractions 4-6 with 1% methanol in chloroform. Fractions 4-6 were combined and evaporated, giving 500 mg of the desired product.

50 Example 325

a-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenemethanol

A 1.45 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was dissolved with stirring in 220 ml of ethanol. A 125 mg portion of sodium borohydride was added and stirring continued for 3 hours. A 63 mg portion of sodium borohydride was added and stirring continued overnight. A 2 ml portion of glacial acetic acid was added and the mixture evaporated. The solid was triturated with water, dried and recrystallized from 30 ml of ethanol giving 710 mg of the desired product, mp 145-147°C.

Example 326

N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethyl]formamide

A mixture of 2.9 g of 1-[3-[[4-(3-pyridinyl]-2-pyrimidinyl]amino]phenyl]ethanone, 40 ml of formamide and 13 ml of concentrated formic acid was refluxed for 15 hours, then cooled and evaporated. The residue was partitioned between unsaturated aqueous potassium bicarbonate and chloroform. The organic phase was separated, dried, filtered and evaporated. The residue was chormatographed on silica gel, eluting 125 ml fractions, fractions 1-4 with chloroform and fractions 5-7 with 2% methanol in chloroform. Fractions 5-7 were combined and evaporated, giving 1.25 g of the desired product as a yellow foam.

Example 327

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2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

A mixture of 35 g of N-(2-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine in 200 ml of 47% aqueous hydrobromic acid was refluxed for 7 hours and then evaporated. The residue was mixed with saturated aqueous potassium bicarbonate and allowed to stand overnight, then filtered. The filtrate was concentrated, giving 3.5 g of the desired compound, mp 166-169°C.

Example 328

N-[3-(1H-Imidazol-1-yl)pheny[]-4-(2-pyridinyl)-2-pyrimidinamine

A solution of 250 ml of 2-acetylpyridine and 500 ml of N.N-dimethylformamide dimethyl acetal was heated on a steam bath for 6 hours. After concentrating the reaction solution under vacuum, 1 liter of hexane was added to the part crystalline residue. The product was collected as small crystalline particles which were washed with an additional liter of hexane. Air drying was followed by drying at 45°C under vacuum, leaving 350.7 g of 3-dimethylamino-1-(2-pyridinyl)-2-propen-1-one.

A mixture of 289.0 g of imidazole, 292 g of potassium carbonate, 3 liters of dimethyl sulfoxide, and 300.0 g of 1-fluoro-3-nitrobenzene was stirred and heated for 25.5 hours between 105-110°C. Then the reaction was poured into 6 liters of water and cooled in the refrigerator over the weekend. The crystalline product was collected and washed with 1 liter of water. Air drying gave 357.6 g of solid. The solid was taken up in 2.4 liters of ethyl acetate and the hot solution passed through hydrous magnesium silicate. After boiling the filtrate down to 1.5 liters, it was cooled to give a precipitate which was collected and washed with 200 ml of ethylacetate, to leave 151.7 g of off-white crystals. After evaporating the mother liquor to dryness, the residue was recrystallized from 350 ml of ethyl acetate to give 59.7 g more product. The mother liquor from the second fraction was evaporated and the residual material recrystallized twice from ethyl acetate to give 30.9 g more product. Total product, 242.3 g of 1-(3-nitrophenyl)-1H-imidazole.

In a Parr hydrogenation bottle was placed 75.00 g of 1-(3-nitrophenyl)-1H-imidazole, 0.70 g platinum oxide, and 250 ml of ethanol. Shaking of this mixture in a Parr hydrogenation apparatus was continued until no more hydrogen was taken up. This process was repeated with 76.33 g of the imidazole, 1.0 g of platinum oxide and 250 ml of ethanol and again with 90.4 g of the imidazole, 1.0 g of platinum oxide and 240 ml of ethanol, until a total of 241.63 g had been reduced. For each batch the catalyst was filtered off and the solvent was removed under vacuum; and then the residues were combined to give 207.2 g of gray crystalline amine. Next the amine was recrystallized from 530 ml of 2-propanol. After collecting the product, it was washed with 200 ml of 2-propanol, and dried, under vacuum, to give 156.4 g of 3-(1H-imidazol-1-yl)benzamine.

A solution of 43.3 g of hydrogen chloride in 290 ml of ethanol was added to 189.0 g of 3-(1<u>H</u>-imidazol-1-yl)benzamine in a 2 liter Erlenmeyer flask. Then 104.7 g of cyanamid was added. The mixture was cautiously warmed in a water bath to an internal temperature of 83°C over 25 minutes. When no exotherm had been noted, the flask was placed inside the steam bath and heated for 2 hours. A final temperature of 97°C was achieved. The resulting brown syrup which was [3-(1<u>H</u>-imidazol-1-yl)phenyl]guanidine, monohydrochloride, was used in the next reaction without further purification.

A mixture of 164 g of potassium carbonate, 209.1 g of 3-dimethylamino-1-(2-pyridyl)-2-propen-1-one, 1.187 mole of crude [3-(1<u>H</u>-imidazol-1-yl)phenyl]guanidine monohydrochloride, and 1 liter of methoxyethanol was stirred and heated under very gentle reflux. A dry-ice condenser filled with water was used to prevent plugging by the dimethylammonium carbonate which is given off by the reaction. The reaction was stopped after 26.5 hours and permitted to stand overnight. A heavy precipitate had formed which was collected as A and washed with 100 ml of ether. The filtrate was concentrated under vacuum as B. Both A and B were triturated with 1.5 liters of water. Then A was washed with 300-400 ml of ethanol, followed by 100 ml of ether to leave, on drying, 172.9 g of gray solid, mp 200-202°C. Recrystallization of B from 150 ml of 2-propanol gave a black solid, C. Next, a classical fractional recrystallization was carried out using methoxyethanol

as the solvent. In the final stages, a large amount of charcoal was added to remove color. In this fashion two main fractions were obtained D, 79.0 g of yellow crystals, mp 204.5-205.5°C, and E, 18.05 g of yellow crystals, mp 204-204.5°C. The yield of D plus E was 26% of the desired product.

EXAMPLE 329

1-(2-Chloroethoxy)-3-nitrobenzene

A mixture of 6.96g. of <u>m</u> - nitrophenol, 100 ml. of 2-butanone, 6.9 g. of potassium carbonate, and 11.74 g. of 2 chloroethyl-tosylate was stirred and heated under reflux for 24 hours. After cooling to room temperature, the salts were filtered off and the filtrate concentrated under vacuum. The residue crystallized on seeding and was recrystallized from carbon tetrachloride to give 8.3 g. of product, m.p. 54.5° - 57° C.

EXAMPLE 330

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1-[2-(3-Nitrophenoxy)ethyl]-1H-imidazole

After dissolving 3.74 g. of imidazole in 60 ml. of dry N,N-dimethylformamide, 1.78 g. of 50% sodium hydride in oil was added. When the effervescence had stopped (circa 1 hr.), 7.35 g. of 1-(2-chloroethoxy)-3-nitrobenzene was added. After stirring overnight, the reaction was concentrated under vacuum. Water was added to the residue and the product was extracted into chloroform. The product was extracted out of the chloroform layer with dilute hydrochloric acid. Next, the aqueous acid layer was neutralized with potassium carbonate and the oily product extracted into chloroform. Upon drying the chloroform extract with sodium sulfate, it was concentrated under vacuum to an oil which crystallized on standing. Recrystallization from isopropyl acetate gave 6.12 g. of product as the monohydrate, m.p. 52.5°-55.5° C.

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EXAMPLE 331

3-[2-(1H-Imidazol-1-yl)ethoxy]benzamine

Using a Parr hydrogenator, 5.00 g. of 1-[2-(3-nitrophenoxy)ethyl]-1H-imidozole in 100 ml. of ethanol and 0.2 g. of platinum oxide was hydrogenated until the hydrogen uptake stopped. The catalyst was filtered off and the filtrate concentrated under vacuum. Several recrystallizations from isopropyl acetate gave 2.8 g. of amine, m.p. 74°-76.5° C.

EXAMPLE 332

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[3-[2-(1H-Imidazol-1-yl)ethoxy]phenyl]-quanidine Dihydrochloride

To a solution of 1.7 g. of hydrogen chloride in 50 ml. of ethanol was added 4.70 g. of 3-[2-(1H-imidazol-1-yl)ethoxy]benzamine in 10 ml. of ethanol. After concentration under vacuum a foam was obtained which gradually crystallized. Next 1.95 g. of cyanamid and 20 ml. of ethanol were added and the mixture heated cautiously, first in a water bath, then directly in a steam bath for a total of 5 hours. A light brown oily guanidine resulted, which was used without purification.

EXAMPLE 333

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3-[2-(4-Morpholinyl)ethoxy]-benzenamine

N-[2-Chloroethyl)morpholine hydrochloride, 80 g., was partitioned between 5N sodium hydroxide and methylene chloride. After drying the organic layer over magnesium sulfate, the solvent was removed under reduced pressure to leave 65 g. of free amine.

To 36.01 g. of m-aminophenol dissolved in 325 ml. of N,N-dimethylformamide, 16.3 g. of 50% sodium hydride in oil was added. The reaction was stirred for 1 hour, until the effervescence stopped; then 57 g. of N-(2-chloroethyl) morpholine, from above, was added. After stirring overnight, the mixture was heated on a steam bath for 1/2 hr., then concentrated under vacuum. The residue was taken up in 300 ml. of 2N hydrochloric acid and washed twice with ether. After basifying with 10N sodium hydroxide, the product was extracted into ether, dried (magnesium sulfate), filtered through hydrous magnesium silicate and evaporated to a brown oil. Distillation gave 34.0 g. of a golden oil, b.p. 165°-180° C./0.45mm.

EXAMPLE 334

[3-[2-(4-Morpholinyl)ethoxylphenyl] quanidine monohydrochloride

Prepared from 3-[2-(4-morpholinyl)ethoxy]-benza-mine by the method of Example 332

EXAMPLE 335

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1-(Bromoacetyl)-4-methylpiperazine monohydrochloride

A solution of 10.0 g. of 1-methyepiperazine in 150 ml of chloroform was cooled in a water bath while 17.3 g. of bromoacetyl chloride in 150 ml. of chloroform was added dropwise, with stirring, over 1/2 hour. A calcium chloride tube protected the reaction from moisture. After stirring overnight, the precipitate was collected and washed with chloroform. The crude product was dried under vacuum at 50° and used as such.

EXAMPLE 336

1-[(4-Aminophenoxy)acetyl]-4-methylpiperazine

20 Prepared from p-aminophenol and 1-(bromoacetyl)-4-methylpiperazine by the method of Example 333 to give a product of m.p. 71°-73° C.

EXAMPLE 337

1-[[4-[(Aminoiminomethyl)amino]phenoxy]acetyl]-4-methylpiperazine Dihydrochloride

Prepared from 1-[(4-aminophenoxy)acetyl]-4-methylpiperazine by the method of Example 332.

TABLE IX

30	Ex.	Acryloyl Source	Phenylguanidine precurser	Product	Mp°C.
	338	Ex. 11	[3-[2-(1H-Imidazol -1-yl)-ethoxy]phenyl]guanidine dihydrochloride	N-[3-[2-(1H-Imidazol-1-yl)ethoxy]phe- nyl-4-(2-pyridinyl) -2-pyrimidinamine	149-151.5
35	339	Ex. 13	[3-[2-(4-morpholinyl)-ethoxy]phe- nyl]guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)ethoxy]phe- nyl]-4-(4-pyridinyl)-2-pyrimidinamine	179-181
	340	Ex. 24	[3-[2-(4-morpholinyl)ethoxy]phe- nyl]guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)ethoxy]phe- nyl]-4-(2-thienyl)-2-pyrimidinamine	134-136
40	341	Ex. 10	[3-[2-(4-morpholinyl)ethoxy]phe- nyl]guanidine monohydrochloride	4-(2-furanyl)-N-[3-[2-(4-morpholi- nyl)ethoxy]phenyl]-2-pyrimidinamine	88-90
	342	Ex. 24	1-[[4-[(Aminoiminome- thyl)amino]phenoxy]acetyl]-4- methyl piperazine dihydrochloride	1-Methyl-4-[[4-(2-thienyl)-2-pyrimidi- nyl]-aminophenoxy]acetylpiperazine	173 175
45	343	Ex. 24	(4-chlorophenyl) guanidine carbonate	N-(4-chlorophenyl) -4-(2-thienyl)-2- pyrimidinamine	185-186
60	344	Ex. 26	[2-[bis(1-methylethyl)amino[ethoxy [guanidine hydrochloride	N-[2-[2-[bis(1-methylethyl) amino]ethoxy] phenyl]-4-(3-pyridinyl)- 2-pyrimidinamine	54-57

The disease diabetes mellitus is characterized by metabolic defects in the production and utilization of glucose which results in the failure to maintain appropriate blood sugar levels. The result of this defect is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and dietary therapies.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is a result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-inde-

pendent diabetes, often occurs in the face of normal, or even elevated, levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin.

The compounds of the present invention and the pharmacologically active acid-addition salts thereof, effectively lower blood glucose levels when administered orally to genetic strains of hyperglycemic mice which are animal models of type II diabetes. The exact mechanism by which they act is not known and the invention should not be construed as limited to any particular mechanism of action. As effective hypoglycemic agents, these compounds are useful for the treatment of hyperglycemia in type II diabetes.

The compounds of this invention were tested for hypoglycemic activity according to the following procedure.

Obese mice [C57 Bl/6J (ob/ob)], their lean littermates (ob/ \pm or +/+) and diabetic mice [C57 Bl/Ks (db/db)] and their non-diabetic littermates (db/+ or +/+) were obtained from Jackson Laboratories, Bar Harbor, Maine. Obese mice were 8 weeks of age and diabetic mice were 9 weeks of age at the start of the test.

The test compounds were dissolved in methanol, mixed with powdered food Purina rodent chow on a weight of compound to weight of chow basis and thoroughly dried.

Groups of 4 control mice received vehicle (methanol) treated chow.

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Groups of 4 test mice were fed ad libitum for one month and food consumption was measured daily (on week days) by weighing the food bins before and after the addition of fresh chow. Thus a 40 g mouse fed the test compound at a concentration of 0.02% of the diet would receive a dose of 20 mg/kg/day if it ate 4 g of chow per day.

Blood samples were collected before the first treatment and once at the end of each week of treatment by retroorbital puncture using the end of each week of treatment by retro-orbital puncture using heparinized capillary tubes. Plasma was separated by centrifugation in a Beckman microfuge for 5 minutes. Plasma glucose concentrations were determined with the Beckman Glucose Analyzer which uses a glucose oxidase method.

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The results of this test on representative compounds of this invention appear in Table X.

TABLE X

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. 55 Effect of Test Compounds on Blood Glucose

28 Glucose Levels in mg/100ml 21 80 166 14 134 148 $\begin{array}{c} 118 \\ 223 \end{array}$ Days 137 160 181 164 166 'n Blood 219 210 209 212 220 21.6 223 214 0 $0.1 \\ 0.1 \\ 0.025$ 0.1 (M/M) Dose 0.1 0.1 ob/ob do/do ob/ob qo/qo qo/qo qo/qo Type of Mice N-(4-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine N-(4-ethylphenyl) -4-(4-pyridinyl)-2-pyrimidinamine N-(4-Ghlorophenyl)-4-(2-Thienyl)-2-pyrimidinanine 4-(2-furanyl)-N-phenyl-2-pyrimidinamine COMPOUND

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40 45	Type of compound	N-[4-(1,1-Dimethylethyl) obphenyl]-4-(4,pyridinyl)-2- obpyrimidingmine obpobyrimidingmine obpob	db db	N[4-(Dimethylamino)phenvl] ol -4-(4-pyridinyl)-2- pyrimidinamine	N-[4-[3-(Dimethylamino)propoxy] phenyl]-4-(3-pyridinyl) -2-pyrimidinamine	N[4-[2-(Diethylamino)ethoxy) phenyl]-4-(3-pyridinyl)-2- pyrimidinamine
. 35	a a	00 00 00 00 00 00 00 00 00 00 00 00 00	db/db db/db db/db	qo/qo	qo/	qo/qo
g g rable X Cont'd.	Dose (W/W)	0.1 0.1 0.1 0.1 0.05	0.1 0.05 0.01	0.1	0.1	0.1
25 P	Blood G	208 214 218 229 225 214	426 429 431	240	215	220
20	11ucos 5	1114 169 1124 118		138	234	191
	Glucose Levels Days 5	175 155 120 139 163	390 314 335		·	
15	in 4	116 143 138	174 293 407			
10	mg/100m1	131 180 181	281 250 400		. ,	·
5	28	135 162	207 270 199			
				T		

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Table X Cont'd

Canob	Type	Dose	Blood	Glucos	e Leve	Blood Glucose Levels in mg/100ml	g/100ml		
-	or Mice	(W/W)	0	5 Days	S.	14	21	28	i
N'-[4-(2-Benzofurnay1)-2- pydmidiny1)-N,N-dimethyl- 1,4-benzenediamīne	qo/qo1	0.1	229 202 223	153 147 144					
N-[4-[2-(Dimethylam-Ino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	ob/ob ob/ob ob/ob ob/ob	0.00	218 228 225 232 230 230	151 144 134	167 148 158 163	128 198 252	155 196 175	140 163 177	
	db/db db/db db/db	0.1 0.05 0.01	369 400 360		410 277 393	403 404 321	328 329 494	222 250 336	
<pre>N=[4-(1H-Imidazol-1- yl)phenyl]4-(4-pyr1- dinyl)-2-pyrimidin- amine</pre>	db/db db/do db/do db/do do/do	0.1 0.1 0.025 0.1 0.1	424 219 210 211 212 219	128	397 200 105 119 158	233 148 140 132 159			
N, N- Diethyl-N ¹ -[4- ob/ob [3-pyridinyl]-2-pyrim-ob/ob idinyl]-1,4-benzene- ob/ob diamine	00/q0 00/q0 00/q0	0.1	223 210 216	138 163 153					

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	Туре	Dose	Blood	Glucos	e Leve	Blood Glucose Levels in mg/100ml	100m1	
COMPOUND	of Mice	8 (M/M)	0	Баув	7	14	21	28
N-{4-(1 - midazo - T-yl)phenyl]-4-(3- pyridinyl]-2-pyrim- idinamine	ob/ob ob/ob ob/op	0.1 0.025 0.1	225 208 210	128	159	171		5 A.A
N-[4-(1H-Imidazol- ob/ob I-yl)phenyl]-4-(2- ob/ob pyridinyl)-2-pyrimią- ob/ob inamine	ob/ob ob/ob ob/ob	0.1	217 223 234	171 167 141				
4-(2-furanyl)-N-[4- (1 <u>H</u> -imidazol-l-yl) phenyl]-2-pyrimidin- amine	ob/ob ob/ob ob/op	0.1 0.025 0.1	227 215 214	137	164	244		·
N-[4-(lH-Imidazol- I-yl)phenyl]-4-(2- thienyl)-2-pyrimid- inamine	ob/ob ob/ob ob/ob ob/ob ob/ob ob/ob ob/ob	0.1 0.025 0.01 0.1 0.1 0.1	221 221 221 224 203 231 218	125 131 126 134	109 147 212 175	116 171 161 161		
	db/db	0.1	423		492	349		

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5		28					
10		in mg/100ml 4 21			·		
15				135	131	·	
		e Levels		157	205		
20	đ	Glucose Days 5	122 147 185 142 211	127 163 135 157	135	236	204
25	Cont'd	Blood 0	219 240 216 229 228	220 237 216 205 210	205 221 244	212	207
30	Table X	Dose 6 (W/W)	00.1 00.1 0.1 0.1	0.1 0.1 0.1 0.1 0.025	0.1 0.025 0.1	0.1	0.1
35							
40		Type of Mice	qo/qo qo/qo qo/qo qo/qo qo/qo	00/q0 q0/q0 q0/q0 q0/q0	qo/qo qo/qo	qo/qo	qo/qo
45		сомроиир	4-[[4-(3-Pyridinyl)- 2-pyrimidinyl]amino] benzenesulfonamide	N-(3-Chlorophenyl)-4 -(4-pyrindinyl)-2- pyrimidinamine	N-(3-Ghlorophenyl)- -4-(3-pyridinyl)-2- pyrimidinamine	N-{4-(4-Methyl-1- Piperazinyl)phenyl) -4(3-pyridinyl)-2- pyrimidinamine	N-(3-Chlorophenyl)- 4-(2-pyridinyl)-2- pyrimidinamine
50		COM	4-[[4- 2-pyri benzen	N- (3-C - (4-py pyrimi	N-(3-G -4-(3- pyrimi	N-[4-(pipera -4(3 pyrimi	N- (3-C 4- (2-'p pyrimi

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Table X Cont'd

	Type	Dose	Blood	61110080	Level	Blood Glucose Levels in mg/100ml	100ml	
COMPOUND	of Mice	(M/N)	0	2	<u> </u>	14	21	2.0
4-(2-furanyl)-N-[4- (4-methyl-1-piper- azinyl)phenyl)-2- pyrimidinamine	ob/ob ob/ob ob/ob	0.1 0.025 0.1	203 210 229	149	179	130		
4-(2-Furanyl)-N- (3-methoxyphenyl) -2-pyrimidinamine	ob/ob ob/ob ob/ob ob/ob	0.1 0.1 0.1 0.1	221 239 217 219	132 113 162 209	•			
N-[4-(4-M2thyl-l- piperazinyl)phenyl] -4-(2-thienyl)-2- pyrimidinamine	ob/ob	0.1	203	1.08				
N-{4-(4-Methyl- I-piperazinvl) ohenyl} -4-(2-pyridinyl) -2- pyrimidinamine	ob/ob	0.1	204	210				

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<i>5</i> .	28	161 202 147 279		·		
10	100ml 21	176 152 178 178				
15	Blood Glucose Levels in mg/100ml Days 14 21	124 200 192 140	134 137 :	·		
	Levels	118 157 130 273	154 171			
20	lucose I Days		125 131 117 130	173	154	153
int و 52	Blood G	204 210 210 406	221 233 226 215 235 223	225	228 215	228
E Table X Contid	Dose &	0.1 0.025 0.01	0.1 0.1 0.1 0.025	0.1	0.1	0.1
35						
40	Type of Mice	qp/qp qo/qo qo/qo	0p/op 0p/op 0p/op 0p/op 0p/op	qo/qo	ob/ob ob/ob mine	qo/qo-
45		- pheny1 1)-2-		N-[3-(1H-Imidazol- I-yl)phenyl]-4- (3-pyridinyl)-2- pyrimidinamine	N-[4-[2-(Diethylamino) ob/eethoxy]phenyl]-4-(2- ob/ethienyl)-2-pyrimidinamine	N-[2-[2-[Bis(1-methyl-ob/obethyl)amino]ethoxy] phenyl]-4-[3- pyridinyl)-2-pyrimid-
50	COMPOUND	N-[4-(4-Methyl]-piperazinyl) -4-(4-pyridiny pyrimidinamine		N-[3-(1H-Imida 1-yl)phenyl]-4 (3-pyridinyl)- pyrimidinamine	N-[4-[2-(ethoxy]p thienyl)	N-[2-[2-[Bis(ethyl)amino]e phenyl]-4-(3- pyridinyl)-2- inamine

Claims

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Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A compound selected from the group consisting of those of the formula:

wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO₂C₂H₅ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl(C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfamilamido, N,N-dialkyl(C_1 - C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formulae:

$$-\text{CO}_{2}\text{R}, -\text{NH}-\text{C}-\text{R}, -\text{NR}-\text{C}-\text{R}, -\text{O}-(\text{CH}_{2})\text{n}-\text{N}_{R},$$

$$-\text{C}-\text{NH}-(\text{CH}_{2})\text{n}-\text{N}_{R}, -\text{CH}-\text{CH}_{3}, -\text{C}-\text{CH}_{3}, -\text{C}-\text{CH}_{3},$$

$$-\text{C}-\text{CH}_{3}, -\text{NH}\text{CH}_{2}-\text{C}-\text{N}_{R}, -\text{N}_{R}$$

$$-\text{CH}_{2}\text{m}-\text{R}_{7}, -\text{X}-(\text{CH}_{2})\text{m}-\text{R}_{7} \text{ and } -\text{X}-\text{CH}_{2}-\text{C}-\text{N}_{R},$$

wherein R is alkyl(C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1 - C_3), alkoxy (C_1 - C_3), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1 - C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1 - C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof.

- 2. The compound according to Claim 1; N-[3-(1H-imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
- 3. The compound according to Claim 1; N-[3-(1H-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine.
- 4. The compound according to Claim 1; N,N-dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine.

- 5. The compound according to Claim 1; N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine.
- The compound according to Claim 1; N-[4-(dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
- The compound according to Claim 1; 4-(2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine.
 - The compound according to Claim 1; N,N-dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, sulfate.
 - The compound according to Claim 1; N-[4-[2-(diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 10. The compound according to Claim 1; 4-(1H-indol-3-yl)-N-phenyl-2-pyrimidinamine.
 - 11. The compound according to Claim 1; N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 15 12. The compound according to Claim 1; N,N-dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydro-chloride
 - 13. The compound according to Claim 1; N-[4-(1H-imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 20 14. The compound according to Claim 1; N-[4-(4-methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
 - 15. The compound according to Claim 1; N-(3-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. A composition of matter in dosage unit form comprising from about 5 mg to about 1500 mg of a compound of Claim
 1 in association with a pharmaceutically acceptable carrier.
 - 17. A process for producing a compound of the formula:

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wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined in claim 1, which comprises condensing an alkanoyl-heteroaryl derivative of the formula:

wherein R_3 and R_4 are as hereinbefore defined with an N,N-di(lower alkyl) formamide or acetamide di (lower alkyl)-acetal at 50°-150°C for 4-24 hours to provide a 3-di(lower alkyl)amino acrylophenone of the formula:

$$R_3$$
-C-C-C-N(lower alkyl)

which is then cyclized with a substituted phenylguanidine of the formula:

HN H2N

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wherein R_1 and R_2 are as hereinbefore defined in an inert organic solvent at the reflux temperature for 6-48 hours.

18. A compound according to claim 1 wherein the compound is:

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine;

N-(4-Ethylphenyl)-6-methyl-4(6-methyl-3-pyridinyl)-2-pyrimidin-amine;

N-(4-Ethylphenyl)-4(-2-pyrazinyl)-2-pyrimidinamine;

N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamine;

N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine;

N-1-Naphthalenyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Phenyl-4-(4-quinolinyl)-2-primidinamine;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

 \underline{N} -(3-Methylphenyl)-4-(1 \underline{H} -pyrrol-2-yl)-2-pyrimidinamine;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-primidinyl]-1,4-benzenediamine;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H -benzimidazol-2-amine;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidozal-2-amine;

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H -benzimidazol-2-amine; or

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine.

Claims for the following Contracting States: ES, GR

A process for producing a compound of the formula

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wherein R₁ is hydrogen, alkyl(C₁-C₃), -COCO₂C₂H₅ or N,N-dimethylaminoethyl; R₂ is mono- or poly-substituted phenyl wherein the substituents are $alkyl(C_1-C_6)$, $alkoxy(C_1-C_3)$, chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl(C1-C3)amino, dialkyl(C1-C3)amino, alkyl(C1-C3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfanilamido, N,N-dialkyl(C₁-C₃)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-

1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formulae:

wherein R is alkyl(C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R₆ is hydrogen, alkyl(C_1 - C_3), alkoxy (C_1 - C_3), chloro, bromo, iodo or trifluoromethyl, R₇ is 1H-imidazol-1-yl or morpholino and R₈ is alkyl(C_1 - C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1 - C_3), halogen or trifluoromethyl; R₃ is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R₄ is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof, said process comprising condensing an alkanoyl-heteroaryl derivative of the formula:

wherein R_3 and R_4 are as hereinbefore defined with an N,N-di(lower alkyl) formamide or acetamide di (lower alkyl)-acetal at 50°-150°C for 4-24 hours to provide a 3-di(lower alkyl)amino acrylophenone of the formula:

$$R_3$$
 -C-C R_5 R₃ -C-C (lower alkyl) R_3

which is then cyclized with a substituted phenylguanidine of the formula:

HN R1

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wherein R₁ and R₂ are as hereinbefore defined in an inert organic solvent at the reflux temperature for 6-48 hours.

2. The process according to Claim 1 for producing N-[3-(1H-imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.

3. The process according to Claim 1 for producing N-[3-(1H-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine.

4. The process according to Claim 1 for producing N,N-dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-ben-zenediamine.

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- 5. The process according to Claim 1 for producing N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine.
- 6. The process according to Claim 1 for producing N-[4-(dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.

7. The process according to Claim 1 for producing 4-(2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine.

8. The process according to Claim 1 for producing N,N-dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, sulfate.

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- 9. The process according to Claim 1 for producing N-[4-[2-(diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
- 10. The process according to Claim 1 for producing 4-(1H-indol-3-yl)-N-phenyl-2-pyrimidinamine.

11. The process according to Claim 1 for producing N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.

12. The process according to Claim 1 for producing N,N-dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride.

- 13. The process according to Claim 1 for producing N-[4-(1H-imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 14. The process according to Claim 1 for producing N-[4-(4-methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.

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- 15. The process according to Claim 1 for producing N-(3-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. The process according to Claim 1 for producing the following compounds

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine;

 $\underline{\text{N-}} \text{(4-Ethylphenyl)-6-methyl-4(6-methyl-3-pyridinyl)-2-pyrimidin-amine;} \\$

N-(4-Ethylphenyl)-4(-2-pyrazinyl)-2-pyrimidinamine;

- N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamine;
- N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine;
- N-1-Naphthalenyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Phenyl-4-(4-quinolinyl)-2-primidinamine;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

N.N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-primidinyl]-1,4-benzenediamine;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H -benzimidazol-2-amine;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidazol-2-amine;

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine;

o Patentansprüche

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Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Verbindung, die aus der Gruppe ausgewählt ist, die aus denjenigen der Formel:

$$\begin{array}{c|c} R_{5} & & R_{1} \\ \hline R_{4} & & R_{3} \end{array}$$

besteht, in der R_1 Wasserstoff, (C_1-C_3) -Alkyl, $-COCO_2C_2H_5$ oder N,N-Dimethylaminoethyl ist; R_2 mono- oder polysubstituiertes Phenyl ist, worin die Substituenten (C_1-C_6) -Alkyl, (C_1-C_3) -Alkoxy, Chlor, Brom, Trifluormethyl, Hydroxy, Phenyl, Amino, (C_1-C_3) -Monoalkylamino, (C_1-C_3) -Dialkylamino, (C_1-C_3) -Alkylketo, Propenyloxy, Carboxyl, Oxyessigsäure, Oxyessigsäureethylester, Sulfanilamido, N,N- (C_1-C_3) -Dialkylsulfanilamido, N-Methylpiperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethylbenzyl oder Einheiten der Formeln:

$$^{NH}_{2}$$
 -CH-CH₃, -NHCH₂-C-N_R, -N R , -N N R $^{$

sind, worin R (C₁-C₃)-Alkyl ist, X Sauerstoff (-O-) oder Schwefel (-S-) ist, m 1 - 3 ist, n 2 oder 3 ist, R₆ Wasserstoff,

(C₁-C₃)-Alkyl, (C₁-C₃)-Alkoxy, Chlor, Brom, lod oder Trifluormethyl ist, R₇ 1H-Imidazol-1-yl oder Morpholino ist und R₈ (C₁-C₃)-Alkyl, Phenyl oder monosubstituiertes Phenyl ist, worin die Substituenten (C₁-C₃)-Alkyl, Halogen oder Trifluormethyl sind; R₃ 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Methyl-3-pyridinyl, 6-Methyl-3-pyridinyl, 2-Furanyl, 5-Methyl-2-furanyl, 2,5-Dimethyl-3-furanyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 2-Pyrazinyl, 2-Benzofuranyl, 2-(Pyridin-N-oxid), 3-(Pyridin-N-oxid), 4-(Pyridin-N-oxid), 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Chinolinyl, 4-Pyridinylmethyliodid, Dimethylaminophenyl oder N-Acetyl-N-methylaminophenyl ist; R₄ Wasserstoff oder (C₁-C₃)-Alkyl ist; und R₅ Wasserstoff oder (C₁-C₃)-Alkyl ist; und die pharmakologisch annehmbaren Säureadditionssalze derselben.

- 10 2. Verbindung nach Anspruch 1: N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
 - 3. Verbindung nach Anspruch 1: N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamin.
 - 4. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamin.
 - 5. Verbindung nach Anspruch 1: N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzoldiamin.
 - 6. Verbindung nach Anspruch 1: N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
- 20 7. Verbindung nach Anspruch 1: 4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamin.
 - 8. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzoldiaminsulfat.
 - 9. Verbindung nach Anspruch 1: N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
 - 10. Verbindung nach Anspruch 1: 4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamin.
 - 11. Verbindung nach Anspruch 1: N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.
- 30 12. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamintrihydrochlorid.
 - 13. Verbindung nach Anspruch 1: N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
 - 14. Verbindung nach Anspruch 1: N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
 - 15. Verbindung nach Anspruch 1: N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.
 - 16. Substanz-Zusammensetzung in Einheitsdosierungsform, umfassend ungefähr 5 mg bis ungefähr 1500 mg einer Verbindung nach Anspruch 1 zusammen mit einem pharmazeutisch annehmbaren Träger.
 - 17. Verfahren zur Herstellung einer Verbindung der Formel:

$$R_5$$
 R_4
 R_3

in der R₁, R₂, R₃, R₄ und R₅ wie in Anspruch 1 definiert sind, umfassend das Kondensieren eines Alkanoylheteroaryl-

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Derivats der Formel:

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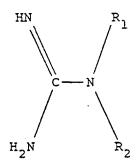
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in der R₃ und R₄ wie vorstehend definiert sind, mit einem N,N-Di(niederalkyl)formamid oder Acetamiddi(niederalkyl)acetal über 4 - 24 Stunden bei 50 - 150°C, um ein 3-Di(niederalkyl)aminoacrylophenon der Formel:

$$R_3$$
 -C-C R_5 R_5 R_3 -C-C (niederalkyl)₂

bereitzustellen, das dann mit einem substituierten Phenylquanidin der Formel:



in der R₁ und R₂ wie vorstehend definiert sind, in einem inerten organischen Lösungsmittel 6 - 48 Stunden bei der Rückflußtemperatur cyclisiert wird.

18. Verbindung nach Anspruch 1, worin die Verbindung ist:

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

40 N-(4-Ethylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(4-pyridinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamin;

45 N-Phenyl-4-(4-chinolinyl)-2-pyrimidinamin;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzoldiamin;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

N-[4-(2-Furanyi)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

oder

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamin.

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Patentansprüche für folgende Vertragsstaaten: ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel:

$$\begin{array}{c|c} R_1 \\ R_5 \\ \hline \\ R_4 \\ \hline \\ R_3 \end{array}$$

in der R_1 Wasserstoff, (C_1-C_3) -Alkyl, $-COCO_2C_2H_5$ oder N,N-Dimethylaminoethyl ist; R_2 mono- oder polysubstituiertes Phenyl ist, worin die Substituenten (C_1-C_6) -Alkyl, (C_1-C_3) -Alkoxy, Chlor, Brom, Trifluormethyl, Hydroxy, Phenyl, Amino, (C_1-C_3) -Monoalkylamino, (C_1-C_3) -Dialkylamino, (C_1-C_3) -Alkylketo, Propenyloxy, Carboxyl, Oxyessigsäure,

Oxyessigsaureethylester, Sulfanilamido, N,N-(C₁-C₃)-Dialkylsulfanilamido, N-Methylpiperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethylbenzyl oder Einheiten der

Formeln:

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sind, worin R (C_1 - C_3)-Alkyl ist, X Sauerstoff (-O-) oder Schwefel (-S-) ist, m 1 - 3 ist, n 2 oder 3 ist, R₆ Wasserstoff, (C_1 - C_3)-Alkyl, (C_1 - C_3)-Alkyl, (C_1 - C_3)-Alkoxy, Chlor, Brom, lod oder Trifluormethyl ist, R₇ 1H-Imidazol-1-yl oder Morpholino ist und R₈ (C_1 - C_3)-Alkyl, Phenyl oder monosubstituiertes Phenyl ist, worin die Substituenten (C_1 - C_3)-Alkyl, Halogen oder Trifluormethyl sind;

R₃ 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Methyl-3-pyridinyl, 6-Methyl-3-pyridinyl, 2-Furanyl, 5-Methyl-2-furanyl, 2,5-Dimethyl-3-furanyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 2-Pyrazinyl, 2-Benzofuranyl, 2-(Pyridin-N-oxid), 3-(Pyridin-N-oxid), 4-(Pyridin-N-oxid), 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Chinolinyl, 4-Pyridinylmethyliodid, Dimethylaminophenyl oder N-Acetyl-N-methylaminophenyl ist; R₄ Wasserstoff oder (C₁-C₃)-Alkyl ist; und der pharmakologisch annehmbaren Säureadditionssalze derselben.

wobei das Verfahren umfaßt:

das Kondensieren eines Alkanoylheteroaryl-Derivats der Formel:

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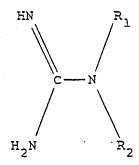
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in der R₃ und R₄ wie vorstehend definiert sind, mit einem N,N-Di(niederalkyl)formamid oder Acetamiddi(niederalkyl)acetal über 4 - 24 Stunden bei 50 - 150°C, um ein 3-Di(niederalkyl)aminoacrylophenon der Formel:

$$R_3$$
-C-C R_5 R_5 R_3 -C-N (niederalkyl)₂

bereitzustellen, das dann mit einem substituierten Phenylguanidin der Formel:



in der $\rm R_1$ und $\rm R_2$ wie vorstehend definiert sind, in einem inerten organischen Lösungsmittel 6 - 48 Stunden bei der Rückflußtemperatur cyclisiert wird.

- 2. Verfahren nach Anspruch 1 zum Herstellen von N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
- 3. Verfahren nach Anspruch 1 zum Herstellen von N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamin.
- 40 4. Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzol-
 - 5. Verfahren nach Anspruch 1 zum Herstellen von N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzol-diamin.
 - 6. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
 - 7. Verfahren nach Anspruch 1 zum Herstellen von 4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamin.
- 50 8. Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzoldiamin-
 - 9. Verfahren nach Anspruch 1 zum Herstellen von N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamin
 - 10. Verfahren nach Anspruch 1 zum Herstellen von 4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamin.
 - 11. Verfahren nach Anspruch 1 zum Herstellen von N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.

- 12. Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamintri-hydrochlorid.
- 13. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
- 14. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
- 15. Verfahren nach Anspruch 1 zum Herstellen von N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.
- 16. Verfahren nach Anspruch 1, das die folgenden Verbindungen erzeugt:

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

N-(4-Ethylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(4-pyridinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Phenyl-4-(4-chinolinyl)-2-pyrimidinamin;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzoldiamin;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamin.

Revendications

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Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Un composé choisi dans la classe formée par ceux de formule :

où R_1 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , - $COCO_2C_2H_5$ ou N_1 -diméthylaminoéthyle ; R_2 est un groupe phényle mono- ou polysubstitué dans lequel les substituants sont des groupes alkyle en C_1 - C_6 , alcoxy en C_1 - C_3 , chloro, bromo, trifluorométhyle, hydroxyle, phényle, amino, mono(alkyle en C_1 - C_3)amino, di(alkyle en C_1 - C_3)amino, (alkyle en C_1 - C_3)céto, propényloxy, carboxyle, acide oxyacétique, ester éthylique d'acide oxyacétique, sulfanilamido, N_1 - N_2 -di(alkyle en N_1 - N_2 - N_3 - N_4 - N_3 - N_4 -

zol-1-yl, 1H-benzimidazol-2-yle, 1-naphtyle, cyclopentyle, 3,4-dimethylbenzyle ou des groupements de formule :

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où R est un groupe alkyle en C_1 - C_3 , X est un atome d'oxygène (-O-) ou de soufre (-S-), m est de 1 à 3, n est 2 ou 3, R_6 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , alcoxy en C_1 - C_3 , chloro, bromo, iodo ou trifluorométhyle, R_7 est un groupe 1H-imidazol-1-yle ou morpholino et R_8 est un groupe alkyle en C_1 - C_3 , phényle ou phényle monosubstitué dont les substituants sont des groupes alkyle en C_1 - C_3 , halogéno ou trifluorométhyle; R_3 est un groupe 2-pyridinyle, 3-pyridinyle, 2-méthyl-3-pyridinyle, 6-méthyl-3-pyridinyle, 2-furanyle, 5-méthyl-2-furanyle, 2,5-diméthyl-3-furanyle, 2-thiényle, 3-thiényle, 5-méthyl-2-thiényle, 2-phénothiazinyle, 2-pyrazinyle, 2-benzofuranyle, 2-(N-oxyde de pyridine), 3-(N-oxyde de pyridine), 4-(N-oxyde de pyridine), 1H-indol-2-yle, 1H-indol-3-yle, 1-méthyl-1H-pyrrol-2-yle, 4-quinolyle, iodure de 4-(N-méthyl) pyridinyle diméthylaminophényle ou N-acétyl-N-méthylaminophényle ; R_4 est un atome d'hydrogène ou un groupe alkyle en C_1 - C_3 ; et R_5 est un atome d'hydrogène ou un groupe alkyle en C_1 - C_3 ; et leurs sels d'addition d'acide pharmacologiquement acceptables.

- Le compose selon la revendication 1 : la N-[3-(1H-imidazol-1-yl)phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
- 3. Le compose selon la revendication 1 : la N-[3-(1H-imidazol-1-yl)phényl]-4-(2-pyridinyl)-2-pyrimidinamine.
- Le composé selon la revendication 1 : la N,N-diméthyl-N-[4-méthyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
- 5. Le composé selon la revendication 1 : la N-[4-(2-furanyl)-5-méthyl-2-pyrimidinyl]-N,N-diméthyl-1,4-benzènedia-
 - 6. Le compose selon la revendication 1 : la N-[4-(diméthylamino)phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 7. Le compose selon la revendication 1 : la 4-(2-furanyl)-N-(3-méthylphényl)-2-pyrimidinamine.
 - Le composé selon la revendication 1 : le sulfate de N,N-diméthyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzènediamine.
 - 9. Le composé selon la revendication : la N-[4-[2-(diéthylamino)éthoxy]phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 10. Le composé selon la revendication 1 : la 4-(1H-indol-3-yl)-N-phényl-2-pyrimidinamine.
 - 11. Le composé selon la revendication 1 : la N-(4-éthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 12. Le composé selon la revendication 1 : le trichlorhydrate de N,N-diméthyl-N-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-ben-zènediamine.
 - 13. Le composé selon la revendication 1 : la N-[4-(1/+imidazol-1-yl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.

- 14. Le composé selon la revendication 1 : la N-[4-(4-méthyl-1-pipérazinyl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 15. Le compose selon la revendication 1 : la N-(3-méthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. Une composition de matière sous forme d'unité posologique comprenant environ 5 mg à environ 1500 mg d'un composé de la revendication 1 en association avec un support pharmaceutiquement acceptable.
 - 17. Un procédé de production d'un composé de la formule :

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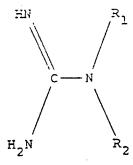
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où R₁, R₂, R₃, R₄ et R₅ sont tels que définis dans la revendication 1, qui comprend la condensation d'un dérivé alcanoyl-hétéroaryle de formule :

où R₃ et R₄ sont tels que définis ci-dessus, avec un acétal de di(alkyle inférieur) de *N,N*-di(alkyle inférieur)formamide ou acétamide entre 50° et 150°C pendant 4 à 24 heures pour produire une 3-di(alkyle inférieur)aminoacrylophénone de formule :

$$\begin{array}{cccc}
 & R_4 & R_5 \\
 & | & | & | & | & | & | & | \\
 & R_3 - C - C \longrightarrow C - N(\text{alkyle inférieur})_2
\end{array}$$

qui est ensuite cyclisée avec une phénylguanidine substituée de formule :



- où R_1 et R_2 sont tels que définis ci-dessus, dans un solvant organique inerte à la température de reflux pendant 6 à 48 heures.
- Un composé selon la revendication 1, dans lequel le composé est : la N-(4-éthylphényl)-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;

la N-(4-éthylphényl)-6-méthyl-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;

la N-(4-éthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-1-naphtalényl-4-(4-pyridinyl)2-pyrimidinamine;

la N-1-naphtalényl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-phényl-4-(4-quinolyl)-2-pyrimidinamine;

la N-phényl-4-(1*H*-pyrrol-2-yl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

la N,N-diméthyl-N-[4-(3-méthyl-2-thiényl)-2-pyrimidinyl]-1,4-benzènediamine;

la N-[4-(2-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole-2-amine;

la N-[4-(2-furanyl)-2-pyrimidinyl]-1 H-benzimidazole-2-amine;

la N-(3-méthoxyphényl)-4-(3-méthyl-2-thiényl)-2-pyrimidinamine;

la N-[4-(2-furanyl)-2-pyrimidinyl]-1 H-benzimidazole-2-amine; ou

la N-(3-méthoxyphényl)-4-(3-méthyl-2-thiényl)-2-pyrimidinamine.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de formule :

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$$\begin{array}{c|c} R_{5} & & R_{1} \\ \hline R_{4} & & N \\ \hline R_{3} & & \end{array}$$

où R est un groupe alkyle en C_1 - C_3 , X est un atome d'oxygène (-O-) ou de soufre (-S-), m est de 1 à 3, n est 2 ou 3, R_6 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , alcoxy en C_1 - C_3 , chloro, bromo, iodo ou trifluorométhyle, R_7 est un groupe 1H-imidazol-1-yle ou morpholino et R_8 est un groupe alkyle en C_1 - C_3 , phényle ou phényle monosubstitué dont les substituants sont des groupes alkyle en C_1 - C_3 , halogéno ou trifluorométhyle ; R_3 est un groupe 2-pyridinyle, 3-pyridinyle, 4-pyridinyle, 2-méthyl-3-pyridinyle, 6-méthyl-3-pyridinyle, 2-furanyle, 5-méthyl-2-furanyle, 2,5-diméthyl-3-furanyle, 2-thiényle, 3-thiényle, 5-méthyl-2-thiényle, 2-phénothiazinyle, 2-pyrazinyle, 2-benzofuranyle, 2-(N-oxyde de pyridine), 3-(N-oxyde de pyridine), 4-(N-oxyde de pyridine), 1H-indol-2-yle, 1H-indol-3-yle, 1-méthyl-1H-pyrrol-2-yle, 4-quinolyle, iodure de 4-(N-méthyl) pyridinyle diméthylaminophényle ou N-acétyl-N-méthylaminophényle ; R_4 est un atome d'hydrogène ou un groupe alkyle en C_1 - C_3 ; et R_5 est un atome d'hydrogène ou un groupe alkyle en C_1 - C_3 ; et leurs sels d'addition d'acide pharmacologiquement acceptables,

ledit procédé comprenant la condensation d'un dérivé alcanoyl-hétéroaryle de formule :

$$R_3$$
-C-CH₂-R₄

où R₃ et R₄ sont tels que définis ci-dessus, avec un acétal de di(alkyle inférieur) de *N,N*-di(alkyle inférieur)formamide ou acétamide entre 50° et 150°C pendant 4 à 24 heures pour produire une 3-di(alkyle inférieur)aminoacrylophénone de formule :

qui est ensuite cyclisée avec une phénylquanidine substituée de formule :

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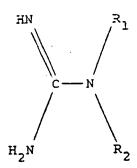
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où R_1 et R_2 sont tels que définis ci-dessus, dans un solvant organique inerte à la température de reflux pendant 6 à 48 heures.

- 2. Procédé selon la revendication 1 pour la préparation de la N-[3-(1H-imidazol-1-yl)phényl]-4-(4-pyridinyl)-2-pyrimidinamine
- Procédé selon la revendication 1 pour la préparation de la N-[3-(1H-imidazol-1-yl)phényl]-4-(2-pyridinyl)-2-pyrimidinamine.
 - 4. Procédé selon la revendication 1 pour la préparation de la N,N-diméthyl-N'-[4-méthyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
 - 5. Procédé selon la revendication 1 pour la préparation de la N'-[4-(2-furanyl)-5-méthyl-2-pyrimidinyl]-N,N-diméthyl-1,4-benzènediamine.

- Procédé selon la revendication 1 pour la préparation de la N-[4-(diméthylamino)phényl]-4-(4-pyridinyl)-2-pyrimidinamine
- 7. Procédé selon la revendication 1 pour la préparation de la 4-(2-furanyl)-N-(3-méthylphényl)-2-pyrimidinamine.
- 8. Procédé selon la revendication 1 pour la préparation du sulfate de N,N-diméthyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzènediamine.
- Procédé selon la revendication 1 pour la préparation de la N-[4-[2-(diéthylamino)éthoxy]phényl]-4-(4-pyridinyl)-2 pyrimidinamine.
 - 10. Procédé selon la revendication 1 pour la préparation de la 4-(1H-indol-3-yl)-N-phényl-2-pyrimidinamine.
 - 11. Procédé selon la revendication 1 pour la préparation de la N-(4(éthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
 - 12. Procédé selon la revendication 1 pour la préparation du trichlorhydrate de N,N-diméthyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
- 13. Procédé selon la revendication 1 pour la préparation de la N-[4-(1H-imidazol-1-yl)phényl]-4-(3-pyridinyl)-2-pyrimi-
 - 14. Procédé selon la revendication 1 pour la préparation de la N-[4-(4-méthyl-1-pipérazinyl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 25 15. Procédé selon la revendication 1 pour la préparation de la N-(3-méthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
 - 16. Procédé selon la revendication 1 pour la préparation des composés suivants :
 - la N-(4-éthylphényl)-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine ;
 - la N-(4-éthylphényl)-6-méthyl-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;
 - la N-(4-éthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;
 - la N-(3-méthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;
 - la N-1-naphtalényl-4-(4-pyridinyl)-2-pyrimidinamine;
 - la N-1-naphtalényl-4-(2-pyridinyl)-2-pyrimidinamine;
 - la N-cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;
 - la N-phényl-4-(4-quinolyl)-2-pyrimidinamine;

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- la N-phényl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;
- la N-(3-méthylphényl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;
- la N, N-diméthyl-N-[4-(3-méthyl-2-thiényl)-2-pyrimidinyl]-1,4-benzènediamine;
- la N-[4-(2-pyridinyl)-2-pyrimidinyl]-1 H-benzimidazole-2-amine;
- la N-[4(-2-furanyl)-2-pyrimidinyl]-1 H-benzimidazole-2-amine;
- la N-(3-méthoxyphényl)-4-(3-méthyl-2-thiényl)-2-pyrimidinamine .

(19)

Europäisches Patentamt European Patent Office Office européen des brevets



) EP 0 233 461 B2

(12)

NEW EUROPEAN PATENT SPECIFICATION

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- (45) Mention of the grant of the patent: 20.03.1996 Bulletin 1996/12
- (21) Application number: 87100277.0
- (22) Date of filing: 12.01.1987
- (54) 4,5,6-Substituted-2-pyrimidinamines
 - 4,5,6-Substituierte 2-Pyrimidinamine
 - 2-Pyrimidinamines substituées en 4,5 et 6
- (84) Designated Contracting States:
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- (43) Date of publication of application: 26.08.1987 Bulletin 1987/35
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 Tal 29
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Description

BRIEF SUMMARY OF THE INVENTION

[0001] This invention relates to organic compounds and, more particularly, is concerned with 4,5,6-substituted-N-(substituted-phenyl)-2-pyrimidinamines having anti-asthmatic activity which may be represented by the following structural formula:

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wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO $_2$ C $_2$ H $_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl-(C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfamilamido, N,N-dialkyl(C_1 - C_3)sulfamilamino, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:

$$-co_2R$$
, $-NH-C-R$, $-NR-C-R$, $-O-(CH_2)n-K_R$,

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$$\begin{array}{c} \mathbb{N}^{\mathrm{H}} \, 2 \\ -\mathrm{CH} - \mathrm{CH}_{3} \, , \quad -\mathrm{NHCH}_{2} - \mathbb{C} - \mathbb{N}_{\mathbb{R}} \end{array} , \quad -\mathbb{N} \\ \end{array}$$

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wherein R is alkyl(C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1 - C_3), alkoxy (C_1 C₃), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1 - C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1 - C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl 4-quinolinyl, 4-pyri-dinyl methyl

iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1 - C_3), and R_5 is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof; with the proviso that when R_1 is hydrogen, R_2 is 4-methylphenyl, R_4 is hydrogen and R_5 is methyl then R_3 is other than 2-furanyl.

[0002] The present invention also includes novel compositions of matter containing the above-defined compounds which are useful for treating asthma, allergic diseases, inflammation and diabetes in mammals. The invention also comprises processes of preparing the compounds within the scope of the above formula. Further, the present invention relates to a specific use of compounds according to claim 19.

[0003] Non-prepublished EP-A-210 044 discloses 2-Amino-4-subst.-5-(hydroxy or alkoxy)pyrimidines useful for the treatment of pulmorary, inflammatory, allergic and cardiovascular diseases.

DETAILED DESCRIPTION OF THE INVENTION

[0004] The novel compounds of the present invention are obtainable as crystalline materials having characteristic melting points and absorption spectra. They are in general sparingly soluble in organic solvents such as lower alkanols, chloroform, tetrahydrofuran, N,N-dimethylformamide, dichloromethane, acetone and the like, but are generally insoluble in water.

[0005] The novel 4,5,6-substituted-2-pyrimidinamines of the present invention in general may be prepared as set forth in the following reaction schemes.

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Scheme I

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wherein R₁, R₂, R₃, R₄ and R₅ are as hereinabove defined.

[0006] In accordance with Scheme I, a heteroaryl (R_3) alkanoyl (R_4) compound 1, e.g 2-acetylpyridine, 2-acetylfuran, 3-acetylthiophene, 2-acetyl-6-methylpyridine, 2-propionyl pyridine or 3-propionyl pyridine and the like, is reacted with a di(lower alkyl)-formamide or acetamide di(lower alkyl) acetal 2, e.g; N,N-dimethylformamide dimethylacetal or N,N-dimethylacetamide dimethylacetal at an elevated temperature in the range of about 50°C. to about 150°C. for from about 4 to 24 hours to produce the 3-di(lower alkyl)aminoacrylophenone 3. The acrylophenone 3 is then reacted with an appropriately substituted phenylguanidine (R_1)(R_2), 4 as the base or as the carbonate, sulfate, nitrate, hydrochloride or dihydrochloride salt in an inert solvent such am absolute ethanol, n-propanol, isopropyl alcohol or 2-methoxyethanol and the like, by heating at the reflux temperature for from 6-48 hours. The product 5 is separated by the partial evaporation of the solvent, then cooling and collected and recrystallized in a conventional manner from solvents such as n-propyl alcohol, isopropyl alcohol, absolute ethyl alcohol or 2-methoxyethanol and the like and combinations of solvents such as chloroform/hexane, dichoromethane/hexane or isopropyl alcohol/ethylene glycol monomethyl ether and

the like.

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Scheme II

wherein R₁, R₂, R₃, R₄ and R₅ are as hereinabove defind.

[0007] In accordance with Scheme II, when the 4,5,6-substituted- 2-pyrimidinamine product $\underline{5}$ is dissolved by heating in a solvent such as absolute ethanol, isopropyl alcohol or dichloromethane, then stirred at room temperature and reacted with a mineral acid such as sulfuric acid, hydrochloric acid, nitric acid or phosphoric acid and the like, dissolved in absolute ethanol or isopropyl alcohol and the like, the 4,5,6-substituted-2-pyrimidinamine acid addition salt $\underline{6}$ is precipitated on standing for 30 minutes and chilling for several hours.

[0008] Alternatively, acid addition salts may be formed with organic acidds such as citric acid or maleic acid and the like by dissolving the desired 4,5,6-substituted-2-pyrimidinamine in hot, absolute ethanol or 2-methoxyethanol in the presence of the organic acid. Cooling provides the desired compounds as solids.

[0009] The novel compounds of the present invention are highly active as antiasthmatic and antiallergic agents as will be demonstrated hereinbelow.

[0010] The bronchospasm of allergic asthma is a consequence of the release of mediators, such as histamine and slow-reacting substances from masts cells. The role of mediator release in the induction of an asthmatic attack has been fully reviewed and documented; see Kaliner, M. and Austen, K. F., Bronchial Asthma Mechanisms and Therepautics, E. B. Weiss, Editor, Little, Brown and Company, Boston, 163, (1976); Lichtenstein, L. M., Asthma-Physiology, Immunopharmacology and Treatment, Second International Symposium, L. M. Lichtenstein and K. F. Austen, Editors, Academic Press, New York, 51, (1979); and Bell, S. C., et al., Annual Reports in Medicinal Chemistry, 14, 51, H. J. Hess, Editor, Academic Press, New York, (1979).

[0011] The novel compounds of this invention have been tested by the procedure of Lichtenstein, L. M. and Osler, A. G., J. Exp. Med., 120, 507-530(1964), which evaluates the ability of compounds to inhibit mediator (histamine) release from immunologically stimulated human basophils.

45 Reagents

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10X Concentrated Tris Buffer

[0012] Dissolve 140.3 g of sodium chloride, 7.45 g of Trizma-Tris Pre-Set, Reagent Grade, pH 7.6, at 25°C (Sigma Chemical Co.) in sufficient water to give a final volume of 2 liters.

Human Albumin

[0013] (Sigma Chemical Co.) (30 mg/ml)

Calcium and Magnesium Stocks

[0014] Made to 0.075 M 0.5 M respectively, with calcium chloride dihydrate and magnesium chloride hexahydrate.

Tris-A Buffer

[0015] A 10 ml portion of 10X Tris Buffer and 1.0 ml of human albumin are diluted to 100 ml with water.

5 Tris ACM Buffer

[0016] A 10 ml portion of 10X Tris Buffer, 1.0 ml of human albumin, 0.8 ml of calcium stock and 0.2 ml of magnesium stock are diluted to 100 ml with water.

10 Rabbit Antihuman IgE

[0017] Behring Diagnostics (Generally used at 10 μg protein/ml final concentration).

House Dust Mite Extract (Dermatophagoides Farinae)

[0018] Strength 1:100 (w:v) allergenic extract, Hollister-Stier Labs. Generally this is diluted 1:1000 to 1:10,000 (considering the vial as stock).

Other Allergens

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[0019] Interdermal solutions or intramuscular preparations for hyposensitization, Hollister-Steir Labs. The final concentration used is on the order of 1 PNU/ml.

Separation of Leukocytes from Human Blood and Challenge

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[0020] Eighty milliliters of blood is withdrawn from subjects with known histamine release to anti-IgE, ragweed antigen or other specific allergen, using four 20 ml heparinized tubes. This 80 ml of blood is mixed with 20 ml of saline containing 0.6 g of dextrose and 1.2 g of dextran. The blood is allowed to sediment at room temperature in two 50 ml polycarbonate centrifuge tubes until a sharp interface develops between the red cells and plasma (60-90 minutes). The plasma (top) layer from each tube is withdrawn by pipet and transferred to respective 50 ml polycarbonate tubes. The plasma is centrifuged for 8 minutes at 110X G at 4°C. The supernatant is carefully poured off as completely as possible and the cell button is resuspended in 2-3 ml of Tris-A buffer using a siliconized Pasteur pipet. The resuspension is accomplished by drawing the liquid gently in an out of the pipet, with the tip below the liquid until an even suspension of cells is obtained. Sufficient Tris-A buffer is then added to bring the volume in the tube to about 45 ml and the tube is centrifuged at 110X G for 8 minutes at 4°C. The supernatant is poured off and the cell button is resuspended and centrifuged as described above. The supernatant is poured off and the cell button is suspended in 2-3 ml of Tris-ACM buffer to make the final volume sufficient to allow addition to the reaction tubes.

[0021] Reaction tubes containing anti-IgE or antigens, either alone or with test compound in a total volume of 0.2 ml are prepared and placed in a 37°C bath. The cells are warmed to 37°C and frequently swirled to ensure an even suspension, while 1.0 ml aliquots are added to each reaction tube. The tubes are then incubated for 60 minutes at 37°C, vortexing the tubes gently every 15 minutes to keep the cells evenly suspended. When the reaction is complete, the tubes are centrifuged at 4°C for 10 minutes at 1500 rpm to sediment the cells. One ml aliquots of supernatant are transferred to 12 mm by 75 mm polyethylene tubes and 0.2 ml of 8% perchloric acid is added to each tube. Blanks and totals are included in each test. The blanks have cells and all reagents except antigen or anti-IgE. The totals contain 0.24 ml of 8% perchloric acid, one ml of cells and 0.2 ml of buffer. All samples are then centrifuged to remove the precipitate protein.

Assay of Released Histamine by the Automated Fluorometric Method

[0022] This automated method has been described by Siraganian, R. P., in Anal. Biochem., <u>57</u>, 383 (1974) and J. Immunol. Methods, <u>7</u>, 283 (1975) and is based on the manual method of Shore, P. A., <u>et al.</u>, J. Pharmacol. Exp. Ther., 217, 182 (1959).

[0023] The automated system consists of the following Technicon Autoanalyzer II components Sampler IV, Dual-Speed Proportioning Pump III, Fluoronephelometer with a narrow pass primary filter 7-60 and a secondary filter 3-74, Recorder, and Digital Printer. The manifold used is the one described by Siraganian vide supra, with the following modifications: the dialyzer is omitted; all pumping tubes pass through a single proportioning pump with large capacity and twice the volume of sample is taken for analysis.

[0024] The automated chemistry consists of the following steps: Extraction from alkaline saline into butanol, back

extraction into dilute hydrochloric acid by addition of heptane, reaction of histamine with <u>o</u>-phthaldialdehyde (OPT) at high pH and conversion of the OPT adduct to a stable fluorophore with phosphoric acid. The reaction product is then passed through the fluorometer. The full scale response is adjusted to 50 ng histamine base with a threshold sensitivity of approximately 0.5 ng.

Calculation of the Results of Histamine Release Tests

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[0025] The instrument blank (wash) is substracted from the ng histamine of each sample. Then the ng histamine of each sample is divided by the mean of the three totals (cells lysed with perchloric acid) to obtain percent release.

[0026] Control samples contain antigen but no test compound. Blank (or spontaneous release) samples contain neither antigen nor test compound. The mean of the blanks (three replicates) is subtracted from the percent release for controls and test compounds.

[0027] The means for control and test compound groups are computed and the result for a test compound is computed as percent of control by the formula:

100 X % Histamine Release with Test Compound % Histamine Release in Controls

[0028] Values obtained at different concentrations of test compound are used to calculate an IC₅₀ (the concentration in μ M which causes a 50% inhibition of histamine release) by linear regression. A compound is considered active if the IC₅₀ is \leq 48 μ M.

[0029] The results of this test on typical compounds of this invention appear in Table I.

TABLE I

IABLE I	
Inhibition of Histamine Release from Immunologically Stimulated Human E	Basophils
Compound	IC ₅₀ (μM)
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine	17.7
4-(4-Pyridinyl)-N-[(3-trifluoromethyl)phenyl]-2-pyrimidinamine	32.0
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.4
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine	0.9
N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.8
N-(4-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(4-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	8.3
N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	1.0
N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	1.9
N-(4-Bromophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	2.3
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, hydrochloride	0.7
4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	2.9
N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	3.9
	<48
N-Phenyl-4-(2-thienyl)-2-pyrimidinamine	31.7
	9.3
N-(3-Methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.7
N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	9.4
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine	0.9
N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.5
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	7.7
N-(4-Ethylphenyl)-5-methyl-4-(4-pyridinyl)-2-pyrimidinamine	<48
N-(4-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	2.1
N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine	0.3
4-(2-Furanyl)-N-phenyl-2-pyrimidinamine	48
4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	3.5

	Inhibition of Histamine Release from Immunologically Stimulated Human Basophils	
7	Compound	IC ₅₀ (μΜ
	I-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	13.4
. 1	N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	19.1
1	N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	<24
	N-(4-Ethylphenyl)-4-pyrazinyl-2-pyrimidinamine	2.8
1	N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimidinamine	5.4
	N-(2-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	3.9
1	N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	10.6
_	N-(2,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	47.1
_	N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	20.2
	N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidinamine	3.8
	N-(2,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	<48
1 -	N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	4.4
	N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine	31.3
	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.0
	N-1-Naphthalenyl-4-(2-pyridinyl-2-pyrimidinamine	3.0
-	N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	24.0
	4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	10.5
	4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidinamine	<48
	N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	<24
	4-(2-Furanyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	<48
	N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidinamine	13.3
_	N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine	2.2
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:	3.5
	1)	
h	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)	1.0
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	3.0
ļi	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate	1.2
ī	N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, pyridine-1-oxide	17.7
i	N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	5.9
i	N-(4-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	15.6
	N-(3-Ethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	9.7
	4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamine	3.0
1	N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	6.9
	N-(3-Methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl) -2-pyrimidinamine	9.4
li	N-(3-Ethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	48.0
	N-(3-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine	1.1
	4-(1H-Indol-2-yl)-N-(3-methylphenyl)-2-pyrimidinamine	2.2
	4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, methyl ester	27.5
	N-(3-Methylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	10.9
	N-Phenyl-4-(-4-quinolinyl)-2-pyrimidinamine	3.0
	N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	4.0
	4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	3.0
	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine, sulfate	3.0
	4-(2-Furanyl)-N-[3-(methylphenyl)]-2-pyrimidinamine, sulfate	3.0
	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate	3.3
٠ ا	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	0.7
	N-(3,5-Dimethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	4.3
	N-(2,4-Difluorophenyl)-4-(4-pridinyl)-2-pyrimidinamine	<48

Compound	IC ₅₀ (μΝ
N-(2,4-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(3-Methylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	1.4
N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	2.9
4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	<48
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	<48
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	2.6
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	3.0
N-[4-(1,1-Dimethylethyl)phenyl]-4-(3-piridinyl)-2-pyrimidinamine	0.7
N-(2,6-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	22.0
N-(4-Ethylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	36.3
N-[(3,4-Dimethyl)methyl]-4-(2-pyridinyl-2-pyrimidinamine	39.8
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sunate N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.0.
N-(3-Methylphenyl)-4-(1 <u>H</u> -pyrrol-2-yl)-2-pyrimidinamine	11.1
4-(5-Methyl-2-furanyl)-N-(3-methylpbenyl)-2-pyrimidinamine	2.0
4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	24.8
N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	3.8
N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	0.4
N-(3-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.2
N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	2.7
N-(3-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.3
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.8
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	12.4
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrintidin-yl]-1,4-benzenediamine	3.7
4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	2.0
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl)benzenediamine, trihydrochloride	0.4
4-(2,5-Dimethyl-3-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	28.5
4-(2,5-Dimethyl-3-furanyl)-N-(3,5-dimethylphenyl-2-pyrimidinamine	4.1
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,4-benzenediamine, dihydrochloride	4.4
4-(2,5-Dimethyl-3-furanyl)-N-(4-ethylphenyl)-2-pyrimidinamihe	19.2
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	1.7
3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester	3.0
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine	0.5
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol	5.1
3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester	20.3
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.2
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	0.6
N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.8
N-[4-(2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	2.7
N'-[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	1.9
N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzendiamine	0.6
N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	4.9
N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	1.8
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	0.3
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	1.5
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	3.5

Inhibition of Histamine Release from Immunologically Stimulated Human Bas	sophils
Compound	IC ₅₀ (μΜ
N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	37.7
N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
N-[4-[2-Diethylamino)ethaxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.2
N-[4-[2-Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	0.5
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid	7.6
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	0.5
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyriziiidin-yl]-1,3-benzenediamine, trihydrochloride	1.0
N-(3,5-Dimethylphenyl)-4-(2-furanyl)-5-methyl-2-pyrimidinamine	<24
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidin-yl]-1,3-benzenediamine, dihydrochloride	0.5
N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	6.1
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	5.0
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	5.6
4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimidinamine	26.8
4-[[4-(4-(Pyridinyl)-2-pyrimidinyl]amino]-phenol	3.3
N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	1.5
N-[4-[2-(Dimethylamino)ethoxy]phenyl]N',N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-	9.1
1,2-ethanediamine	1.3
N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.2
4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium, iodide	33.3
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl)]-1,3-benzenediamine, sulfate	1.0
N,N-Dimethyl-N'-[4-(4-pyridinyr)-2-pyrimidinyr]-1,3-benzenediamine	2.4
	1.6
N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,3-benzenediamine	<24
	0.8
N-(2-(Diethylamino)ethyl)-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide 4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenoxy]acetic acid, ethyl ester	5.8
N,N-Diethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.1
N,N-Dimethyl-N'-[4-nethyl-6-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	31.8
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	12.3
N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, hydrochloride	3.0
N,N-Diethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.7
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.3
1-[4-[7-imidazoi-1-yi)prieriyi]-4-(3-pyridiriyi)-2-pyrimidirariine	11.4
1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethanone, 0.methyloxime	5.1
N,N-Diethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	10.1
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrinidinamine	1.8
4-(2-Furanyl)-N-[4-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	2.2
N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-benzamide	4.6
N,N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	5.7
N,N-Dimethyl-N'-[4-(3-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	2.1
N-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	0.4
N-[4-[1-Aminoethyl])phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	0.8
4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.2
N-(3-Chlorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	3.1
N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimidnamine	1.5
N-(3-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	1.7
N-Methyl-N-[4-([4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyi]acetamide	1.1
N-Methyl-N-[4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	0.1

Compound .	IC ₅₀ (μΝ
N-Methyl-N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl)amino]phenyl]acetamide	0.6
[4-(2-Furanyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	0.3
4-(2-Benzofuranyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	1.2
Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]-amino]acetic acid, ethyl ester	2.1
N-[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.3
N,N-Dirnethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	40
N-(4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	3.6
4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-benzenesulfonamide	4.5
N-[4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	1.5
N-(3-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	0.9
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.5
N-(3-Methoxyphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	2.3
N-(3-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.3
4-(2-Furanyl)-N-(1-[4-methyl-1-piperazinyl)-phenyl]-2-pyrimidinamine	1.8
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.6
N-(3-Methoxyphenyl)-4-(2,5-dimethyl-3-furanyl)-2-pyrimidinamine	5.8
N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	1.0
N-(3-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	0.7
N-(3-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	3.3
N-(3-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.9
1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethanone	4.1
N-Methyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4 -benzenediamine	2.1
N-[4-(1-Methylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.1
N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.4
N-(3-Ethyiphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.7
N-(3-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.4
3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.7
3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.2
N-[4-(1,1-Dimethylethyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	4.6
N,N-Diethyl-N'-[4-(2-furanyl)-2-pyrimidinyl]-1,4-benzenediamine	3.4
3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-benzenesulfonanide	0.5
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-benzenediamine, fumarate	36.2
2-[1-[4-[3-Pyridinyl)-2-pyrimidinyl]amino] phenyl]ethylidene]hydrazinecarboxamide	8.1
N-[4-[2-[bis(1,1-Dimethylethyl)amino]ethoxy]-phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	4.6
α -Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]benzenemethanol	4.5
N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	4.6
N-[3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	2.1
N-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.0
N- [4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	0.4
N,N-Diethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]1,4-benzenediamine	28.0
N-(3-Methoxyphenyl)4-(5-methyl-2-furanyl)-2-pyrimidinamine	1.2
N-[3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.3
N-[3-(1H-Imidazol-1-y1)phenyl]-4-(2-pyridinyl)-2-pyrinidinamine	0.1
N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	1.0
N-[2-Methyl-4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl)acetanide	1.2
2-Methyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	0.9
N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	0.2
N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-amino]phenyl]acetamide	0.3

TABLE I (continued)

Inhibition of Histamine Release from Immunologically Stimulated Human	Basophils
Compound	IC ₅₀ (μM)
N-[3-(1-Aminoethyl)phenyl)-4-(3-pyridinyl)-2-pyrimidinanine, trihydrochloride	5.1
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	2.8
N-(2-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	9.8
N-[4-[[4-(2-Thienyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.2
N-[2-Methyl-4-(4-(3-pyridinyl)-2-pyrimidinyl]-phenyl]acetamide	1.8
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N diethyl-1,4-benzenediamine	6.2
N-[4-[[4-(2-Furanyl)-2-pyrimidinyl] amino]-phenyl]acetamide	0.7
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.4
N-[3-(1H-lmidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.1
2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenol	23.5
4-(2-Furanyl)-N-[3-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	0.8
N-[3-[2-(Diethylamino]ethoxy]phenyl]-4-(2-furanyl)-2-pyrimidinamine	1.3
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl]-4-(2-pyridinyl)-2-pyrimidinanine	1.6
N-[3-[2-(Diethylaniino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.6
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.7
N-[4-(4-Pyridinyl)-2-pyrimidinyl)-1,4-benzenediamine	2.4
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	· 0.4
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.2

[0030] The ability of these compounds to inhibit lipoxygenase activity in terms of the suppression of the release and biosynthesis of leukotriene B4(LTB4) and 5-hydroxy-eicosatetraenoic acid (5-HETE) was measured as follows.

[0031] In this assay $3x10^7$ peritoneal neutrophils derived from guinea pigs were incubated at 37° C in Dulbeccos buffer containing 50mM tris buffer (pH 7.4). Five minutes before the addition of 100 μ M arachidonic acid and 20 μ M calcium ionophore (A23187), control vehicle or the test compounds were added to the neutrophils at a concentration of 10 μ g/ml.

[0032] Three minutes after the addition of arachidonic acid and calcium ionophore the total lipid was partitioned into chloroform after adjusting the pH to 3 with citric acid and the addition of equal parts of methanol and chloroform.

[0033] The 5-HETE and LTB4 were resolved by HPLC using a 5 μ M 4x25 cm octadecyl silica column (IBM Instruments) with 70-80% methanol in water adjusted to pH 3.0 with acetic acid. As the mobile phase was pumped at 1.0 ml/minute, LTB4 and 5-HETE were detected by absorbance at 270 and 236 nm, respectively.

[0034] LTB4 and 5-HETE were quantitated by comparison with the control and the results were expressed as a percent of control. The lower the percentage, the more active the compound.

[0035] The results of this test on representative compounds of this invention appear in Table II.

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TABLE II

IABLE II						
Inhibition of Neutrophil Lipoxygenase from Immunologically Stimulated Guinea Pig Neutrophiles						
Compound	% Inhibition					
	LTB4	5-HETE				
4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	58.1					
N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine		37.0				
N-(4-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine		45.0				
N-(4-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		45.0				
N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine		53.0				
4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine		58.0				
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine		58.0				
		40.0				
	33.9	41.0				
N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	29.5	41.0				
	Inhibition of Neutrophil Lipoxygenase from Immunologically Stimulated Guinea Pig Compound 4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine N-(4-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine N-(4-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine 4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine N-[4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	Compound Westerophile				

Inhibition of Neutrophil Lipoxygenase from Immunologically Stimulate	ed Guinea Pig Neutrophile	<u></u>	
Compound % Inhi			
	LTB4	5-HETE	
4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	7.4	3.0	
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	46.0		
N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	53.4	54.0	
N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimidinamine		50.0	
N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyriaddinaadne	36.4	28.7	
N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	58.4		
N-Phenyl-4-(3-thienyl)-2-pyrimidinamine		56.0	
N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidinamine		48.0	
N-(4-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine		56.0	
N-(2,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine		54.0	
N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	53.1	54.0	
N-(2-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	17.4	21.0	
N-(2,5-Dimethoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	43.2	47.0	
N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinanine	37.0	43.0	
N-(2-Methoxy-5-methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	•	54.0	
4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	53.6		
4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidinamine		44.0	
4-(2-Furanyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	45.0	49.0	
N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidinamine	33.0		
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-	58.0		
1,2,3-propanetricarboxylate (2:1)			
\underline{N} -[(3,4-Dimethylphenyl)methyl]-4-(4-pyridinyl)-2-pyrimidinamine	24.0	36.0	
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	56.0		
4-(2-Benzofuranyl)- <u>N</u> -(3-methylphenyl)-2-pyrimidinamine	46.1		
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		19.0	
\underline{N} -(3,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		19.0	
N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	17.3	35.0	
N-(4-Fluorophenyl)-4-(3-thienyl)-2-pyrimidinamine	51.6	İ	
4-(10H-Phenothiazin-2-yl)-N-phenyl-2-pyrimidinamine		48.0	
4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamine	41.2	39.0	
N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	44.7	37.0	
N-(3-Methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine		60.0	
4-(1-Methyl-1H-pyrrol-2-yl)-N-phenyl-2-pyrimidinamine		57.0	
N-(4-Ethylphenyl)-4-(1H-indol-3-yl)-2-pyrimidinamine	56.5		
N-[1,1'-Biphenyl]-4-yl-(4-pyridinyl)-2-pyrimidinamine	37.1	45.0	
4-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]-benzoic acid, methyl ester	45.2	47.0	
N-(3-Hethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	16.0		
N-Phenyl-4-(4-quinolinyl)-2-pyrimidinamine	46.4	57.0	
N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine		58.0	
N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	56.1		
N-[4-(1,1-Dimethylethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	47.8	54.0	
N-Methyl-N-phenyl-4-(2-pyridinyl)-2-pyrimidinamine	58.1	54.0	
N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	55.4		
N-(4-Ethylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	32.6	54.0	
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)-phenyl]-2-pyrimidinamine sulfate	37.3	49.0	
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	48.0	43.0	
4-(3-Methyl-2-thienyl)-N-phenyl-2-pyrimidinamine		59.0	

TABLE II (continued)

_							
	Inhibition of Neutrophil Lipoxygenase from Immunologically Stimulated Guinea Pig Neutrophiles						
	Compound	% Inhibition					
5		LTB4	5-HETE				
-	4-(5-Methyl-2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	59.6					
	4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	42.3	52.0				
	N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	16.6	12.4				
10	N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	31.2	50.0				
	N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	20.1	17.2				
	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	50.7	56.0				
	4-[[4-13-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	35.8	47.0				
	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	43.4	34.0				
15	4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	46.9	56.0				
ŀ	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	40.7	37.0				
	N.N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	37.6	39.0				
	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenol		30.0				
20	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	36.1	50.0				
•	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	50.0					
	N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	34.1	•				
	N'[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	16.9	16.9				
	N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	49.8	17.8				
25	N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	21.6	17.0				
	N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl-1,4-benzenediamine	16.4	13.6				
	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	46.8	42.0				
	N,N-Diniethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	51.1					
30	N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.6	10.0				
	N-(3,5-Dimethylphenyl)-4-methyl-6-(3-pyridinyl)-2-pyrimidinamine	32.7	40.0				
	N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzendiamine	3.6					
	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	52.4					
	N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	22.9	30.0				
35	4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimidinamine	30.3	42.0				
	4-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]-phenol	. ,	36.0				
	N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridinyl-2-pyrimidinamine	57.4					
	N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	39.6	50.0				
40	N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	31.1	37.7				
	N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	24.1	53.6				
	N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	34.0					
	N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]anino]phenyl]acetamide	51.0	46.0				
	N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-diethyl-1,4-benzenediamine	51.0	45.0				
45	N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)phenyl)-4-(4-pyridinyl)-2-pyrimidinamine	20.0	16.0				
	N-[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	47.0	28.0				
	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	50.0	51.0				
	N-[3-(1H-Imidazolyl)phenyl]-4-(2'-thienyl)-2-pyrimidinamine	50.0	39.0				
50	N-[4-(2-Furanyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride		54.0				
77	N-([4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine		19.0				
	4-[[4-(2-Furanyl)-2-pyrimidinyl)amino]-benzenesulfonamide	47.0					

[0036] The novel compounds of the present invention are effective as antiasthmatic agents in mammals when administered in amounts ranging from about 0.1 mg to about 100 mg/kg of body weight per day. A preferred dosage regimen for optimum results would be from about 0.1 mg to about 25 mg/kg of body weight per day, and such dosage units are employed that a total of from about 7 mg to about 1.8 g of the active compound for a subject of about 70 kg

of body weight are adminstered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that these active compounds may be administered in any convenient manner such as by the oral, aerosol, intravenous, intramuscular, or subcutaneous routes.

[0037] The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets or they may be incorporated directly with the food of the diet. For oral therapeutic administration, these active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 200 mg of active compound.

[0038] The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially nontoxic in the amounts used. In addition, these active compounds may be incorporated into sustained-release preparations and formulations.

[0039] Compositions according to the present invention having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.10% to 10.0% by weight of active compound in a vehicle consisting of a polyhydric aliphatic alcohol or mixtures thereof. Especially satisfactory are glycerin, propylene glycol, and polyethylene glycols. The polyethylene glycols consist of a mixture of non-volatile, normally liquid, polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from about 200 to 1500. Although various mixtures of the aforementioned non-volatile polyethylene glycols may be employed, it is preferred to use a mixture having an average molecular weight of from about 200 to about 400.

[0040] In addition to the active compound, the parenteral solutions may also contain various preservatives which may be used to prevent bacterial and fungal contamination. The preservatives which may be used for these purposes are, for example, myristyl-gamma-picolinium chloride, benzalkonium chloride, phenethyl alcohol, p-chlorophenyl-al-pha-glycerol ether, methyl and propyl parabens, and thimerosal. As a practical matter, it is also convenient to employ antioxidants. Suitable antioxidants include, for example, sodium bisulfite, sodium metabisulfite, and sodium formaldehyde sulfoxylate. Generally, from about 0.05% to about 0.2% concentrations of anti-oxidant are employed.

[0041] These compounds may also be administered by inhalation using conventional Aerosol® formulations.

[0042] The invention will be described in greater detail in conjunction with the following specific examples.

Example 1

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4-(3-Pyridinyl-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine

[0043] A 7.04 g amount of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 18.72 g of [3-(trifluoromethyl)phenyl]guanidine carbonate in 500 ml of <u>n</u>-propanol was heated at reflux temperature for 16 hours. The solvent was evaporated to near dryness, then water was added and the precipitate which formed was collected by filtration, then recrystallized from hexane to give 5.55 g of the desired product, mp 170-171 °C.

Example 2

N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine

[0044] A mixture of 14.4 g of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one and 16.1 g of 4-methoxyphenyl guanidine carbonate in 200 ml of isopropanol was heated at reflux for 20 hours. The reaction mixture was cooled, the crude product was collected by filtration and washed with water. The material was recrystallized from isopropanol to

give the desired product as light yellow crystals, mp 121-122°C.

Example 3

5 N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine

[0045] A 14.4 g amount of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 16.1 g of 4-methoxyphenylguanidine carbonate in 200 ml of isopropanol was heated at reflux for 24 hours. The solvent was evaporated to 1/3 volume, then the mixture was cooled in an ice-bath to crystallize the crude product. The product was collected by filtration and washed with water, then with isopropanol. The material was recrystallized from isopropanol/ethylene glycol monomethyl ether to give 16.7 g of the desired product as yellow crystals, mp 174-175°C.

Example 4

15 N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine

[0046] A mixture of 10.9 g of 3-dimethylamino-1-(2-thienyl)-2-propen-1-one (U. S. Patent 4,374,988) and 11.8 g of 4-methoxyphenylguanidine carbonate in 150 ml of isopropanol was heated at reflux for 48 hours. The solution was cooled, then filtered, giving 9.0 g of the desired product as yellow crystals, mp 158-160°C.

Example 5

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4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, methyl ester

[0047] A solution of 10.0 g of 4-guanidinobenzoic acid, hydrochloride in 310 ml of methanol was mixed with 6.0 ml (9.68 g) of thionyl chloride at 0°C for 15 minutes, then stirred for one hour at room temperature and then heated at reflux for 16 hours. The solvent ws removed in vacuo and the solid was washed with ether and air dried to give 11.4 g of white crystals (A).

[0048] The above procedure was repeated using 20.0 g of 4-guanidinobenzoic acid, 11.9 ml (19.4 g) of thionyl chloride and 600 ml of methanol to give 22.6 g of white crystals (B).

[0049] The products (A) and (B) were combined and recrystallized from absolute ethanol. The product was washed with cold absolute ethanol and air dried giving 26.2 g of p-guanidinobenzoic acid, methyl ester, hydrochloride as white crystals, mp 137-138.5°C (dec.).

[0050] A 9.15 g amount of the above compound was partially dissolved in 100 ml of methanol (stored over 4A molecular sieves) and 2.15 g of sodium methoxide was added. The mixture was stirred briefly, then 7.0 g of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one was added and the mixture was heated under argon with stirring for 21.5 hours. The reaction mixture was cooled in an ice bath, then filtered and washed with cold methanol. The residue was dissolved in a mixture of dichloromethane and methanol and filtered to remove sodium chloride. The filtrate was concentrated on a steam bath until crystal formation. The mixture was allowed to stand at room temperature for 16 hours then was filtered. The precipitate was washed with ice cold methanol then dried and gave 5.8 g of the desired product, mp 194.5-196.5°C.

Example 6

45 3-Dimethylamino-1-(3-indolyl)-2-propen-1-one

[0051] A mixture of 3.18 g of 3-acetylindole and 5.17 ml (4.36 g) of <u>tert</u>-butoxybis(dimethylamino)methane was heated on a steam bath for 4 hours. The cooled reaction mixture was triturated with <u>n</u>-hexanes and gave a semi-solid. The solvent was removed <u>in vacuo</u> and the material was triturated with dichloromethane giving 3.08 g of the desired compound as a tan crystalline solid, mp 239-245°C.

Example 7

3-Dimethylamino-1-(5-methyl-2-thienyl)-2-propen-1-one

[0052] A mixture of 56.08 g of 2-acetyl-5-methylthiophene and 250 ml of N,N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16 hours. The mixture was cooled in an ice bath and filtered giving 66.82 g of the desired compound, mp 118-121°C.

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Example 8

3-(Dimethylamino)-1-(5-methyl-2-furanyl-2-propen-1-one

5 [0053] A mixture of 37.24 g of 2-acetyl-5-methylfuran and 150 ml of N,N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16.5 hours. The solvent was removed in vacuo and the residue taken up in dichloromethane and passed through a short column of magnesium silicate. The filtrate was evaporated on a steam bath with the addition of n-hexanes to a volume of 100-150 ml. Cooling with scratching gave 28.31 g of the desired compound, mp 123-125°C.

Example 9

3-(Dimethylamino)-1-(1H-pyrrol-2-yl)-(E)-2-propen-1-one

15 [0054] A mixture of 39.6 g of 2-acetylpyrrole and 104 ml (87.7 g) of tert-butoxy bis(dimethylamino)methane was heated on a steam bath for 20 minutes. The reaction was allowed to subside, then heating was continued for 6 hours. The mixture solidified then was slurried in hexane with chilling. The crude product was collected, washed with hexane and dried. The solid was dissolved in chloroform containing 5% methanol and filtered through magnesium silicate. The eluent was evaporated in vacuo and the residue was recrystallized from dichloromethane/hexane containing a small amount of methanol. The solid was collected, washed with hexane then dried in vacuo giving 25.1 g of the desired compound as yellow crystals, mp 192-193°C (dec.).

[0055] The following 3-(dimethylamino)acrylophenone intermediate compounds listed in Table III were prepared in a similar manner to the procedures described in Examples 6-8 and by those described in U. S. Patents 4,281,000 4,374,988 and in Case 29,240, Serial number 672,753, filed on November 19,1984.

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TABLE III

3-(Dimethylamino)acrylophenone Intermediates

Ex.	R ₃	R4	Rs	WPOC
10	2-Furanyl	H	H	84-86
11	2-pyridinyl	Ħ	H	127-130
12	2-furanyl	CH ₃	H	Oil
13	4-pyridinyl	Œ3	H	106-108
14	6-methyl-3- pyridinyl	H	H	116-118
15	6-methyl-3- pyridinyl	H	CH ₃	119-120
16	2-pyrazinyl	Ħ	Ħ	132-133
17	3-thienyl	H	H	89-90
18	4-quinolinyl	Ħ	Ħ	
19	3-methyl-2- thienyl	Ħ	Ħ	45-49
20	l-methyl-l <u>H</u> - pyrrol-2-yl	Ħ	H	94-95
21	5-methyl-2- thienyl	H	CH3	123-126
22	2,5-dimethyl- 3-furanyl	Ħ	B	91-95
23	2-pyridinyl	Ħ	C∄3	68-70

TABLE III (continued)

Ex.	R ₃	R4	R ₅	WPOC
24	2-thienyl	н	сн3	97-99
25	4-pyridinyl	н	CH3	88-89
26	3-pyridinyl	H	CH3	62-64
27	3-pyridinyl	CH3	H -	76-78
28	3-methyl-2- pyridinyl	В	Ħ	97-98
29	2-benzo- furanyl	H	H	137.0-138.5
30	3-pyridinyl	H	H	97-99
31	2-pheno- thiazine	H	Ħ	

30 Examples 32-251

4,5,6-Substituted-2-pyrimidinamines

[0056] The following 4,5,6-substituted-2-pyridinamine final products listed in Table IV were obtained by reacting a 3-(dimethylamino)acrylophenone from Table III and an appropriately substituted phenylguanidine base, carbonate, sulfate, nitrate or hydrochloride salt in an inert solvent such as absolute ethanol, n-propanol, isopropanol, 2-methoxyethanol, or n-butanol and the like, with or without a base such as sodium hydroxide, potassium hydroxide or potassium carbonate and the bike by heating at the reflux temperature for from 6-90 hours, then recovering the product in a $conventional\ manner\ with\ recrystallization\ from\ solvents\ such\ as\ \underline{n}-propanol,\ is opropanol,\ absolute\ ethanol\ and\ the\ like.$

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TABLE IV

2-Amino-4,5,6-substituted Pyrimidinamines

Dodw .	141-142	198-200	147-148	181-183	167-169	162-164	186-188
Product	Phenylguanidine carbonate 4-(2-Puranyl)-5-methyl-W-phenyl-2-pyrimidinamine	4-(4-Pyridinyl)-N-[3-(trifluoro-methyl)phenyl]-2-pyrimidinamine	Phenylguanidine carbonate N-Phenyl-4-(3-pyridinyl)-2-pyrimi- dinamine	(4-Acetylphenyl)guanidine N-(4-Acetylphenyl)-4-(3-pyridinyl)-	(4-Fluorophenyl)guanidine $\frac{N-(4-Fluorophenyl)-4-(3-pyridinyl)-5}{2-pyrimidinamine}$	N(4-Methoxyphenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	(4-Fluorophenyl)guanidine N-(4-Fluorophenyl)-4-(4-pyridinyl)-carbonate
Phenylguanidine Precursor	Phenylguanidine carbonate	<pre>{3-(Trifluoromethyl)- phenyl]guanidine carbon- ate</pre>	Phenylguanidine carbonate	(4-Acetylphenyl)guanidine	(4-Fluorophenyl)guanidine carbonate	(4-Methoxyphenyl)guani- dine_carbonate	(4-Fluorophenyl)guanidine carbonate
Acrylophenone Source	Бх. 12	Бж. 3	8x. 1	Ex. 1	Bx. 1	Ex. 11	Ex. 3
BX.	32	33	34	35	36	37	8 .

	Acr	Phe		
EX.	sonice	FEGULEOF	Product	MPoC
39	Ex. 1	(4-Bromophenyl)guanidine carbonate	N-(4-Bromophenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	174-175
Ş	Ex. 4	(4-Fluorophenyl)quanidine carbonate	4-Fluorophenyl)quanidine N-(4-Fluorophenyl)-4-(2-thienyl)-2-arbonate	176-178
7	Bx. 11	[3-(Trifluoromethyl)- phenyl}guanidine carbon- ate	4-(2-Pyridinyl)-N-[3-(trifluoro-methyl)phenyl]-2-pyrimidinamine	161-162
42	Bx. 4	Phenylguanidine carbonate	Phenylguanidine carbonate M-Phenyl-4-(2-thienyl)-2-pyrimidin-	137-139
Ç	Ex. 1	3-Chloro-4-methylphenyl- guanidine carbonate	N-(3-Chloro-4-methylphenyl)-4-(3- Pyridinyl)-2-pyrimidinamine	140-145
=	Bx. 11	3-Methylphenylguanidine carbonate	$\frac{N}{2}$ -pyrimidinamine	135-137
45	Ex. 3	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-pyridinyl)- 2-pyrimidinamine	157-159

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m X	Acrylophenone Source	enone ;e	Phenylguanidine Precursor	Product	MPOC
46	EX.	m	Phenylguanidine carbonate	henylguanidine carbonate N-Phenyl-1-(4-pyridinyl)-2-pyrimi- dinamine	153-154
47	EX.	-	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(3-pyridinyl)- Z-pyrimidinamine	102-103
₩	× ×	m	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(4-pyridinyl)- Z-pyrimidinamine	138-140
4	Ex.	13	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-5-methyl-4-(4- Pyridinyl)-2-pyrimidinamine	132-133
20	Ex.	.	3,4-Dichlorophenylguani- dine carbonate	N-(3,4-Dichlorophenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	214-216
51	Bx.	~	4-Bthylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(3-pyridinyl)- Z-pyrimidinamine	120-122.5
52	Bx.	11	4-Bthylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	148.5-149.5

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Acrylophenone Phenylguanidine Source Precursor			Product	MPoC
Ex. 4 3-Methylphenylguanidine N-(3-Methy Carbonate	-Methylphenylguanidine Arbonate	N-(3-Methy 2-pyrimidi	N-(3-Methylphenyl)-4-(2-thlenyl)- Z-pyrimidinamine	112.5-114.5
Ex. 10 Phenylguanidine carbonate 4-(2-Furanyl)-N-phenyl-2-pyrimidin-	Phenylguanidine carbonate 4-(2-Fura amine	4-(2-Pura amino	nyl)- <u>N</u> -phenyl-2-pyrimidin-	144~145
Ex. 10 3-Mathylphenylguanidine 4-(2-Furanyl)-N-carbonate 2-pyrimidinamine	-Methylphenylguanidine arbonate	4-(2-Puri 2-pyrimi	4-(2-Puranyl)-N-(3-methylphenyl)- 2-pyrimidinamine	98~99.5
Ex. 14 4-Ethylphenylguanidine N-(4-Eth carbonate pyridiny	-Ethylphenylguanidine arbonate	N-(4-Eth Pyridiny	N-(4-Ethylphenyl)-4-(6-methyl-3- Pyridinyl)-2-pyrimidinamine	154-155
Ex. 15 4-Ethylphenylguanidine N-(4-Eth carbonate methyl-:	-Ethylphenylguanidine arbonate	N-(4-Et) methyl-: amine	N-(4-Ethylphenyl)-6-methyl-4-(6- methyl-3-pyridinyl)-2-pyrimidin- amine	118-120
Ex. 16 4-Ethylphenylguanidine N(4-Ethylpheny pyrimidinamine	-Ethylphenylguanidine arbonate	N(4-Bthy Pyrimid	N(4-Bthylphenyl)-4 -(2-pyrazinyl)-2- pyrimidinamine	157.5-159
Ex. 16 3-Methylphenylguanidine N-(3-Me 2-pyrim	-Methylphenylguanidine arbonate	N-(3-Me 2-pyrim	N-(3-Methylphenyl)-4-(2-pyrezinyl)- Z-pyrimidinamine	112.5-117

TABLE IV (continued)

Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
09	Вх. 3	2-Methylphenylguanidine carbonate	N-(2-Methylphenyl)-4-pyrazinyl)-2- pyrimidinamine	129~130.5
61	Вх. 3	3-Ethylphenylquanidine sulfate	N-(3-Ethylphenyl)-4-(4-pyridinyl)- Z-pyrimidinamine	126-128
62	Ex. 3	2,5-Dimethylphenylguani- dine carbonate	N-(2,5-Dimethylphenyl)-4-(4-pyri- dinyl-2-pyrimidinemine	131-134
6	Ex. 3	2,3-Dimethylhenylguani- dine carbonate	N-(2,3-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	121-123
64	Ex. 17	3-Nethylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(3-thienyl)- Z-pyrimidinamine	104.5-105.5
65	Ex. 11	2,5-Dimethylphenylguani- dine carbonate	N-(2,5-Dimethylphenyl)-4-(2-pyri- dinyl)-2-pyrimidinamine	139-142
99	Ex. 3	3,5-Dimethylphenylguani- dine carbonate	N-(3,5-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	183-185

Bx.	Acrylophenone Source	Phenylguanidine Frecursor	Product	MPoC
67	Вх. 3	l-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(4-pyridinyl)- Z-pyrimidinamine	174-176
89	Ex. 11	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2- Pyridinyl)-2-pyrimidinamine	114-119
69	8x. 11	l-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(2-pyridinyl)- Z-pyrimidinamine	135-138
70	Ex. 3	2,4-Dimethylphenylguani- dine carbonate	N-(2,4-Dimethylphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	116-118
71	Ех. 3	2,4,6-Trimethylphenyl-guanidine carbonate	4-(4-Pyridinyl)-N-(2,4,6-trimethyl-phenyl)-2-pyrimidinamine	142-144
72	Ex. 10	4-Methoxyphenylguanidine carbonate	4-(2-Furany1)-N-(4-methoxypheny1)- 2-pyrimidinamine	155-158.5
73	Вх. 10	[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	4-(2-Furanyl)-N-[3-(trifluorometh- yl)phenyl]-2-pyrimidinamine	150-154

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158-160.5

96-98.5

130-133.5

Ex.

	MPOC	150-152	106-109	130-133.	158-160.	95-98	188-190	96-98.5
TABLE IV (continued)	Product	N-(4-Fluorophenyl)-4-(2-furanyl)- Z-pyrimidinamine	N-Cyclopentyl-4-(2-pyridinyl)-2- pyrimidinamine	N-(3,4-Dimethylphenyl)-4-(2-pyri- dinyl)-2-pyrimidinamine	N-(4-Methoxyphenyl)-4-(3-thienyl)- Z-pyrimidinamine	N-(3-Ethylphenyl)-4-(2-furanyl)-2- pyrimidinamine	Phenylguanidine carbonate 4-(1H-Indol-3-yl)-N-phenyl-2-phenyl-2-pyrimidinamine	2-Methoxy-5-methylphenyl- N-(2-Methoxy-5-methylphenyl)-4-(4-guanidine carbonate pyridinyl)-2-pyrimidinamine
TABLE IV	Phenylguanidine Precursor	4-Fluorophenylguanidine carbonate	N-Cyclopentylguanidine sulfate	3,4-Dimethylphenylguani- dine carbonate	4-Methoxyphenylguanidine carbonate	3-Bthylphenylguanidine sulfate	Phenylguanidine carbonate	2-Methoxy-5-methylphenyl- guanidine carbonate
	Acrylophenone Source	Бж. 10	Bx. 11	Bx. 11	Ex. 17	Ex. 10	8x. 6	Ex. 3

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Βx.	Acrylophenone Source	nenone Se	Phenylguanidine Precursor	Product	MPOC
8	Ex. 20	20	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(1-methyl-1H- pyrrol-2-yl)-2-pyrimidinamine	117-120
93	æ ×	20	4-Bthylphenylquanidine carbonate	N-(4-Ethylphenyl)-4-(1-methyl-1 <u>H</u> - Pyrrol-2-yl)-2-pyrimidinamine	89-91
83	Ex. 20	20	Phenylguanidine carbonate	Phenylguanidine carbonate $4-(1-Methyl-1H-pyrrol-2-yl)-M-phenyl-2-pyrimidinamine$	118-120
8 .	Ex.	4	3-Bthylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(2-thlenyl)-2- pyrimidinamine	114-116
8.5	Ex.	17	3-Bthylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(3-thienyl)- 2-pyrimidinamine	86-89
96	Ex.	9	3-Methylphenylguanidine carbonate	4-(1H-Indol-2-yl)-N-(3-methylphen- yl)-2-pyrimidinamine	164-167
87	Ex.	18	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-quinolin- yl)-2-pyrimidinamine	196-198
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Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPOC
88	Ex. 18	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-4-(4-quinolinyl)-2-pyrimi-	182-184
89	Ex. 16	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(4-quinolinyl)- Z-pyrimidinamine	176-178
90	Ex. 10	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2-fur- anyl)-2-pyrimidinamine	126-129.
16	Ex. 4	3,5-Dimethylphenylguani- dine hydrochloride	\overline{N} -(3,5-Dimethylphenyl)-4-(2-thien- \overline{Y} 1)-2-pyrimidinamine	152-155
92	Бх. 3	N-Methyl-N-phenylguani- dine hydrochloride	N-Methyl-N-phenyl-4-(4-pyridinyl)- Z-pyrimidinamine	105-107
9	8x. 3	2,4-Difluorophenylguani- dine hydrochloride	N-(2,4-Difluorophenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	172-174
94	Ex. 1	2,4-Difluorophenylguani- dine hydrochloride	N-(2,4-Difluorophenyl)-4-(3-pyri-dinyl)-2-pyrimidinamine	163-165

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Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
95	Ex. 7	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	114-116
96	Вх. 3	2,6-Difluorophenylguani- dine hydrochloride	N-(2,6-Difluorophenyl)-4-(4-pyrl-dinyl)-2-pyrimidinamine	174-176
97	Вх. 9	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-4-(1H-pyrrol-2-yl)-2-	154-157
86	Ex. 1	4-Tert-butylphenylguani- dine sulfate	N-[4-(1,1-Dimethylethyl)phenyl]-4- [3-pyridinyl]-2-pyrimidinamine	130-133
66	Ex. 1	2,6-Difluorophenylguani- dine hydrochloride	N-(2,6-Difluorophenyl)-4-(3-pyri- dinyl)-2-pyrimidinamine	163-166
00.	Ex. 7	3,5-Dimethylhenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(5-methyl- Z-thienyl)-2-pyrimidinamine	133-135
101	Ex. 7	4-Ethylphenylguanidine carbonate	N-(4-Bthylphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	123-125

Ex.	Acrylophenone Source	ne Phenylguanidine Precursor	Product	MPOC
102	Ex. 11	3,4-Dimethylphenylguani- dine hydrochloride	N-[(3,4-Dimethylphenyl)methyl]-4- [2-pyridinyl]-2-pyrimidinamine	158-160
103	Ex. 7	3,5-Dimethylphenylquani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(3-methyl- Z-thienyl)-2-pyrimidinamine	151-155
104	Ex. 9	3-Methylphenylguanidine carbonate	$\frac{N}{Y}$ 1)-2-pyrimidinamine	129-130
1.05	Ex. 8	3-Methylphenylguanidine carbonate	4-(5-Methyl-2-furanyl)-N-(3-meth- ylphenyl)-2-pyrimidinamine	119-121
106	Ex. 21	Phenylguanidine carbonate	Phenylguanidine carbonate 4-Methyl-6-(5-methyl-2-thlenyl)-N-	133-135
107	Вк. 3	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N-[4-(Dimethylamino)phenyl]-4-(4-guanidine dihydrochloride pyridinyl)-2-pyrimidinamine	164-166
108	Ex. 3	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(4-pyri- dinyl)-2-pyrimidinamine	159-160

Bx.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPOC
109	Ex. 11	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-pyridin- yl)-2-pyrimidinamine	110-113
110	Ex. 11	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N-[4-(Dimethylamino)phenyl]-4-(2-guanidine dihydrochloride pyridinyl)-2-pyrimidinamine	171-174
111	Ex. 1	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(3-pyridin- yl)-2-pyrimidinamine	126-127
112	Ex. 1	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-(3-pyri-dinyl)-2-pyrimidinamine	125-128
113	Ex. 1	4-(Ethoxycarbonyl)phenyl- guanidine hydrochloride	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]benzoic acid, ethyl ester	197-202
114	Ex. 1	4-(Dimethylamino)phenyl- quanidine dihydrochloride	N.N-Dimethyl-N'-[4-(3-pyridinyl)- Z-pyrimidinyl]-l,4-benzenediamine	165-166
115	Bx. 22	Phenylguanidine carbonate	Phenylguanidine carbonate 4-(2,5-Dimethyl-3-furanyl)- <u>N</u> -phenyl-2-pyrimidinamine	116-118

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EX.	Acrylophenone Source	Phenylguanidine Precursor	Product	МРОС
116	Ex. 17	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(3-thienyl)-2- Pyrimidinamine	151-152.5
117	Ex. 22	3-Methylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	144-146
118	Ex. 22	3,5-Dimethylphenylguani-	4-(2,5-Dimethyl-3-furanyl)- N -(3,5-dimethylphenyl)-2-pyrimidinamine	149-152
119	Ex. 22	4-Bthylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(4- ethylphenyl)-2-pyrimidinamine	93-96
120	Ex. 1	3-Dimethylaminophenyl- guanidine dihydrochloride	3-Dimethylaminophenyl N.N-Dimethyl N'-[4-(3-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-I,3-benzenediamine	123-125
121	Ex. 11	3-(Bthoxycarbonyl)phenyl- guanidine hydrochloride	3-(Rthoxycarbonyl)phenyl- 3-[[4-(2-Pyridinyl)-2-pyrimidinyl]- guanidine hydrochloride amino]benzoic acid, ethyl ester	156-158
122	Ex. 11	3-(Dimethylamino)phenyl- guanidine dihydrochloride	3-(Dimethylamino)phenyl- N.N-Dimethyl-N'-[4-(2-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-I,3-benzenediamine	109-111

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Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
123	Ex. 1	3-(Ethoxycarbonyl)phenyl- guanidine hydrochloride	3-(Ethoxycarbonyl)phenyl- guanidine hydrochloride amino)benzolc acid, ethyl ester	95-103
124	Ex. 10	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N'-[4-(2-Furanyl)-2-pyrimidinyl]- guanidine dihydrochloride N.N-dimethyl-1,4-benzenediamine	166-167
125	EX.	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N.N-Dimethyl-N'-[4-(2-thienyl)-2-guanidine dihydrochloride pyrimidinyl)-l'.4-benzenediamine	174-175
126	Bx. 22	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- N'-[4-(2,5-Dimethyl-3-furanyl)-2-guanidine dihydrochloride pyrimidinyl]-N'N-dimethyl-1,4-benzenedlamine	126-129
127	Ex. 19	4-(Dimethylamino)phenyl- guanidine dihydrochloride	N, N-Dimethyl-N'-[4-(3-methyl-2-thlenyl)-2-pyrimidinyl]-1,4-benzenediamine	145-148
128	Ex. 3	3-(Dimethylamino)phenyl- guanidine dihydrochloride	3-(Dimethylamino)phenyl- N.N-Dimethyl-N'-[4-(4-pyridinyl)-2-guanidine dihydrochloride pyrimidinyl]-I,3-benzenediamine	165-168
129	Ex. 12	3,5-Dimethylphenylguani~ dine	N-(3,5-Dimethylphenyl)-4-(2-fur-anyl)-5-methyl-2-pyrimidinamine	155-158

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Ex.	Acrylophenone Source	enone	Phenylguanidine Precursor	Product	MPoc
130	0 BX.	12	4-(Dimethylamino)phenyl- guanidine dihydrochloride	$N' = \{4 - \{2 - Purany1\} - 5 - methy1 - 2 - pyrimidiny1\} - N'N-dimethy1 - 1,4 - benzenediamine$	146-148
131	X X	29	4-(Dimethylamino)phenyl- guanidine dihydrochloride	4-(Dimethylamino)phenyl- guanidine dihydrochloride dinyl]-N,N-dimethyl-l,4-benzene- diamine	175-178
132	Ex.	11	2-Guanidinobenzimidazole	N-{4-(2-Pyridinyl)-2-pyrimidinyl}- IH-benzimidazol-2-amine	276-279.5
132	EX.	23	Phenylguanidine carbonate	4-Methyl-N-phenyl-6-(2-pyridinyl)- 2-pyrimidinamine	94-98
134	Ex.	4	3-(Dimethylamino)phenyl- guanidine dihydrochloride	$\frac{N}{N}$ -Dimethyl-N'-[4-(2-thienyl)-2- Pyrimidinyl]- $\frac{N}{N}$ -benzenediamine	118-120
135	BX.	&	3-(Dimethylamino)phenyl- quanidine dihydrochloride	N,N-Dimethyl-N'-[4-(5-methyl-2- furanyl)-2-pyrimidinyl]-1,3-ben- zenediamine	126-129
136	Ex.	22	3-(Dimethylamino)phenyl- guanidine dihydrochloride	N'-{4-(2,5-Dimethyl-3-furanyl)-2- pyrimidinyl)-N.N-dimethyl-1,3- benzenediamine	153-155
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Ex.	Acrylophenone Source	Phenylguanidine Frecursor	Product	MPOC
137	Ex. 3	4-Aminoacetylphenylguani- dine hydrochloride	-Aminoacetylphenylguani - N-[4-[[4-(4-Pyridinyl]-2-pyrimidin- ine hydrochloride yl]amino]phenyl]acetamide	294-296
138	Бх. 3	4-(Diethylamino)phenyl- guanidine dihydrochloride	N.N-Diethyl-N'-[4-(4-pyridinyl)- Z-pyrimidinyl]-l,4-benzenediamine	126-128
139	8x. 1	4-(Diethylamino)phenyl- guanidine dihydrochloride	N,N-Diethyl-N'-[4-(3-pyridinyl)- Z-pyrimidinyl]-l,4-benzenediamine	100-104
140	Ex. 17	Phenylguanidine carbonate	Phenylguanidine carbonate N-Phenyl-4-(3-thienyl)-2-pyrimidin-amine	142-143
141	8x. 11	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	207-209
142	Вх. 11	4-Chlorophenylguanidine carbonate	N-(4-Chlorophenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	220-222
143	Бж. 3	4-Methylphenylguanidine carbonate	N-(4-Methylphenyl)-4-(4-pyridinyl)- 197.5-198.5 Z-pyrimidinamine	197.5-198.5

BX.	Acrylophenone Source	e Phenylguanidine Precursor	Product	MP ^O C
144	Ex. 31	N-[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	4-(2-Phenothiazine)-N-[3-(tri- fluoromethyl)phenyl]-2-pyrimidin- amine	240-243
145	Ex. 31	4-Methoxyphenylguanidine carbonate	N-(4-Methoxyphenyl)-4-(2-pheno- thiazine)-2-pyrimidinamine	220-225
146	Ex. 31	3,4-Dichlorophenylguani- dine carbonate	N-(3,4-Dichlorophenyl)-4-(2-pheno- thiazine)-2-pyrimidinamine	235-238
147	Ex. 11	2,4-Dimethylphenylguani-dine carbonate	N-(2,4-Dimethylphenyl)-4-(2-pyri- dinyl)-2-pyrimidinamine	111.5-113.5
148	Ex. 3	2-Methoxyphenylguanidine carbonate	N-(2-Methoxyphenyl)-4-(4-pyridin-yl)-2-pyrimidinamine	112-117
149	Ex. 3	2,5-Dimethoxyphenylguani- dine carbonate	,5-Dimethoxyphenylguani- N-(2,5-Dimethoxyphenyl)-4-(4-pyri-	151.5-155.0
150	Ex. 11	2-Methoxy-5-methylphenyl- guanidine carbonate	:-Methoxy-5-methylphenyl- $\frac{N}{N}$ -(2-Methoxy-5-methylphenyl)-4-(2-juanidine carbonate pyridinyl)-2-pyrimidinamine	117-1:8.5

Bx.	Acrylophenone Source	Phenylguanidine: Precursor	Product	MPOC
151	Вх. 3	3,4-Dimethylphenylguani- dine hydrochloride	N-[(3,4-Dimethylphenyl)methyl]-4- [4-pyridinyl)-2-pyrimidinamine	132-136
152	Ex. 29	3-Methylphenylguanidine carbonate	4-(2-Benzofuranyl)-N-(3-methyl-phenyl)-2-pyrimidinamine	143-144
153	Bx. 3	3,4-Dimethylphenylguani- dine carbonate	N-(3,4-Dimethylphenyl)-4-(4-pyrl- dinyl)-2-pyrimidinamine	169-171.5
154	Bx. 17	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(3-thienyl)- Z-pyrimidinamine	185-187
155	Ех. 31	Phenylguanidine carbonate	Phenylguanidine carbonate 4-(10H-Phenothiazin-2-y1)-N-phenyl-2-pyrimidinamine	218-220
156	Bx. 6	4-Bthylphenylguanidine carbonate	N-(4-8thylphenyl)-4-(lH-indol-3-Yl)-2-pyrimidinamine	209-210
157	Бх. 3	1,1'-Biphenylguanidine hydrochloride	N-[1,1'-Biphenyl]-4-yl-4-(4-pyrl- dinyl)-2-pyrimidinamine	203-205

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2	Acrylophenone	enone	Phenylguanidine Fraction	tonpord	COGE
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158	EX.	m	[4-(1,1-Dimethylethyl)- phenyl]guanidine sulfate	N-{4-(1,1-Dimethylethyl)phenyl}- 4-(4-pyridinyl)-2-pyrimidinamine	181-183
159	EX.	11	N-Methyl-N-phenylguani- dine hydrochloride	N-Methyl-N-phenyl-4-(2-pyridinyl)- 2-pyrimidinamine	88-91
160	EX.	6	4-Bthylphenylguanidine carbonate	\overline{N} -(4-Bthylphenyl)-4-(1 <u>H</u> -pyrrol-2- \overline{Y} l)-2-pyrimidinamine	131-133
161	BX.	19	Phenylguanidine carbonate	Phenylguanidine carbonate 4-(3-Methyl-2-thlenyl)-N-phenyl-2-pyrimidinamine	137-140
162	×	25	4-Dimethylaminophenyl- guanidine dihydrochloride	N.N-Dimethyl-N'-[4-methyl-6-(4- pyridinyl)-2-pyrimidinyl]-1,4- benzenediamine	153-154
163	Ex.	56	3,5-Dimethylphenylguani- dine hydrochloride	N-(3,5-Dimethylphenyl)-4-methyl-6- (3-pyridinyl)-2-pyrimidinamine	136-140
164	X X	12	N-[3-(Trifluoromethyl)- phenyl]guanidine carbon- ate	4-(2-Furanyl)-5-methyl-N-[3-(tri-fluoromethyl)phenyl]-2-pyrimidin- amine	169-171

BX.	Acrylophenone Source	none	Phenylguanidine Precursor	Product	MPOC
165	Ex. 23	3	N-(3,5-Dimethylphenyl)- guanidine	N-(3,5-Dimethylphenyl)-4-methyl-6- [2-pyridinyl)-2-pyrimidinamine	110-112
166	Ex. 10		2-Guanidinobenzimidazole	N-{4-(2-Furanyl)-2-pyrimidinyl}- I <u>H</u> -benzimidazol-2-amine	306.5-308
167	Bx. 23	е	N-[4-(Dimethylamino)- phenyl]guanidine dihydro- chloride	N.N-Dimethyl-N'-[4-methyl-6-(2- pyridinyl)-2-pyrimidinyl]-1,4- benzenediamine	145-148
168	Вх. 3		4-(1-Imidazolyl)phenyl- guanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4- [4-pyridinyl)-2-pyrimidinamine	>320
169	Вх. 30	0	4-(1-Imidazolyl)phenyl- guanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4- [3-pyridinyl)-2-pyrimidinamine	134-174 (Dec.)
170	Bx. 1	_	N-[4-Diethylamino)phen- yl]guanidine dihydro- chloride	$N,N-Diethyl-N'-\{4-(2-pyridinyl)-2-pyrimidinyl]-l,4-benzenediamine$	138-139
171	Ex. 1	-	4-(1-Imidazoly1)pheny1- guanidine dihydrochloride	4-(1-Imidazoly1)pheny1- N-(4-(1H-Imidazol-1-y1)pheny1)-4-guanidine dihydrochloride (2-pyridiny1)-2-pyrimidinamine	204-206

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Ex.	Acrylophenone Source	Phenylguanidina Precursor	Product	MPoc
172	Ex. 10	4-(1-Imidazoly1)phenyl- guanidine dihydrochloride	4-(1-Imidazoly1)phenyl- 4-(2-Furany1)-N-[4-(1H-imidazol-1-guanidine dihydrochloride yl)phenyl]-2-pyrimidinamine	211-212.5
173	Ех. 12	N-{3-Dimethylamino)phen- yl]guanidine dihydro- chloride	N.N-Dimethyl-N'-[4-(2-furanyl)-5- methyl-2-pyrimidinyl]-1,3-benzene- diamine	154-156
174	Ex. 21	N-{3-Dimethylamino)phen- yl]guanidine dihydro- chloride	N,N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-l,3-ben-zenediamine	130-133
175	Ex. 17	N-(4-(Dimethylamino)- phenyl jguanidine dihydro- chloride	$N.N-Dimethyl-N'-\{4-(3-thienyl)-2-pyrimidinyl\}-1,4-benzenediamine.$	173-174
176	Ex. 13	N-[3-(Dimethylamino)phen- y1)guanidine dihydro- chloride	N.N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl]-1,3-benzenediemine	200-201
771	8×.	4-(1-Imidazolyl)phenyl- guanidine hydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4- [2-thienyl]-2-pyrimidinamine	179~189 (Dec.)
178	Ex. 19	N-(3-Methoxyphenyl)guani- dine hydrochloride	-(3-Methoxyphenyl)guani-N-(3-Methoxyphenyl)-4-(3-methyl-2- lne hydrochloride	120-123
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æx.	Acrylophenone Source	enone	Phenylguanidine Precursor	Product	MPOC
279	Bx.	30	N-[4-[Acetylamino]phen- yl]guanidine hydrochlor- ide	N-[4-[[4-(3-Pyridiny])-2-pyrimidin- Yl]amino]phenyl]acetamide	192-195
1 8.0	ж ж	30	N-(4-Benzenesulfonamido)- guanidine hydrochloride	N-(4-Benzenesulfonamido)- 4-[[4-(3-Pyridiny1)-2-pyrimidinyi]-guanidine hydrochloride	224-225
181	× S	<u>س</u>	N-(3-Chlorophenyl)guani- dine carbonate	N-(3-Chlorophenyl)-4-(4-pyrldinyl)- Z-pyrimidinamine	160-161
162	χ ×	30	N-(3-Chlorophenyl)guani- dine carbonate	N-(3-Chlorophenyl)-4-(3-pyridinyl)- Z-pyrimidinamine	146-148
183	æ ×	17	N-(3-Methoxyphenyl)guani- dine hydrochloride	$\frac{N-(3-Methoxypheny1)guan1-}{3}$ $\frac{N-(3-Methoxypheny1)-4-(3-thieny1)-}{2}$ $\frac{7}{2}$ - Pyrimidinamine	142-145
184	×	. 4	N-(3-Methoxyphenyl)guani- dine hydrochloride	N-(3-Methoxyphenyl)guani- N-(3-Methoxyphenyl)-4-(2-thlenyl)- dine hydrochloride 2-thlenyl)-	151-153
185	EX.	30	[4-(acetylmethylamino)phenyl] guanidine hydrochloride	N-Methyl-N-[4-[[4-(3-pyrldinyl)-2- Pyrimidinyl]emino]phenyl]acetamide	194-197

TABLE IV (continued)

Acrylophenone Phenylguanidi Ex. 3 [4-(acetylmethylami -quanidine hydrochl 187 Ex. 11 [4-(acetylmethylami -quanidine hydrochl -quanidine hydrochl -quanidine hydrochloric 188 Ex. 10 N-(3-Methoxypheny dine hydrochloric 189 Ex. 29 N-(3-Methoxypheny dine hydrochloric 191 Ex. 3 N-Acetylphenylgue 192 Ex. 10 N,N-Dimethylphenylgue dine dihydrochloric dine dihydrochloric			
Ex. 3 Ex. 10 Ex. 29 Ex. 9 Ex. 9 Ex. 3	Phe	Product	MPoC
Ex. 10 Ex. 29 Ex. 9 Ex. 3 Ex. 3	[4-(acetylmethylamino)pheny -guanidine hydrochloride	[4-(acetylmethylamino)phenyl] N-Methyl-N-[4-[(4-pyridinyl)-2-quanidine hydrochloride pyrimidinyl]amino]phenyl]acetamide	233-234
Ex. 10 Ex. 29 Ex. 9 Ex. 3	[4-(acetylmethylamino)phenyl] -guanidine hydrochloride	1] N-Methyl-N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	179-181
Ex. 29 Ex. 3 Ex. 3	N-(3-Methoxyphenyl)guan dine hydrochloride	N-(3-Methoxyphenyl)guani- 4-(2-Furanyl)-N-(3-methoxyphenyl)- 4-(2-Furanyl)-N-(3-methoxyphenyl)- 2-pyrimidinamine	114-116
Ex. 9 Ex. 10	N-(3-Methoxyphenyl)guan dine hydrochloride	N-(3-Methoxyphenyl)guani- 4-(2-Benzofuranyl)-N-(3-methoxy-dine hydrochloride phenyl)-2-pyrimidinamine	137
Ex. 3 Ex. 10	N-(Ethylphenyl)guanidine Carbonate	e N-(4-Ethylphenyl)-4-(1-methyl-lii- pyrrol-2-yl)-2-pyrimidinamine	89-91
Ex. 10	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(4-Pyriciny])-2-pyrimi- dinyl]amino]phenyl]acetamide	294-296
	N.NDimethylphenylguani- dine dihydrochloride	- N.N-Dimethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	154-156

TABLE IV (continued)

Acrylophenone Frecur Source 193 Ex. 30 N-Acetylpheny hydrochloride 194 Ex. 11 Sulfonylamino guanidine hyd guanidine hydrochloride 195 Ex. 11 N-Acetylpheny hydrochloride 197 Ex. 30 4-(4-Methylpheny hydrochloride) 198 Ex. 7 3-Methoxyphen hydrochloride 199 Ex. 11 3-Chloropheny hydrochloride			
Ex. 30 Ex. 11 Ex. 4 Ex. 4 Ex. 30 Ex. 7	Phenylguanidine Frecursor	Product	MPOC
Ex. 11 Ex. 4 Ex. 4 Ex. 30 Ex. 7 Ex. 7	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(3-Pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	192-195
Ex. 11 Ex. 4 Ex. 30 Ex. 7 Ex. 7	Sulfonylaminophenyl- guanidine hydrochloride	4-[[4-(2-Pyridinyl]-2-pyrimidinyl]- amino]benzenesulfonamide	274-277
Ex. 4 Ex. 30 Ex. 7 Ex. 11	N-Acetylphenylguanidine hydrochloride	N-[4-[4-(2-Pyridinyl)-2-pyrimidin- yl]amino]phenyl]acetamide	254-255
Ex. 30 Ex. 7 Ex. 11	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-thienyl)- Z-pyrimidinamine	151-153
Ex. 7 Ex. 11	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(3-pyridinyl)-2-pyrimi- dinamine	174-175
Bx. 11	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2- thienyl)-2-pyrimidinamine	149-151
	3-Chlorophenylguanidine hydrochloride	N-(3-Chlorophenyl)-4-(2-pyridinyl)- Z-pyrimidinamine	164-165

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPoC
200	Вж. 10	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	4-(2-Furanyl)-N-[4-(4-methyl-1- piperazinyl)phenyl]-2-pyrimidin- amine	193-195
201	8x. 4	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(2-thienyl)-2-pyrimidin- amine	215.5-216.5
202	Bx. 11	4-(4-Methylpiperazin-l- yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-l-piperazinyl)- phenyl]-4-(2-pyridinyl)-2-pyrimi- dinamine	192-193

TABLE IV (continued)

Ä	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
203	Ex. 13	4-(4-Methylpiperazin-1- yl)phenylguanidine dihydrochlorido	N-[4-(4-Methyl-1-piperazinyl)- phenyl]-4-(4-pyridinyl)-2- pyrimidinamine	207-209
204	Ex. 22	<pre>3-Mathoxyphenylguani- dine hydrochloride</pre>	N-(3-Methoxyphenyl)-4-(2,5-dimeth- yl-3-furanyl)-2-pyrimidinamine	124-125
205	Ех. 13	J-Fluorophenylguani- dine hydrochloride	N-(3-Fluorophenyl)-4-(4-pyridinyl)- 2-pyrimidinamine	162
206	Ех. 30	1-Fluorophenylguani- dine hydrochloride	N-(3-Fluorophenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	147-150
207	Ex. 11	1-Fluorophenylguani- dine hydrochloride	N-(3-Fluorophenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	162-164
208	Ex. 10	4-Acotylphonylguani- dine	<pre>1-[3-[4-(3-Pyridinyl).2-pyrimi- dinyl]amino]phenyl]ethanone</pre>	166-168

TABLE IV (continued)

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	Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C	
	209	Ех. 30	1-(Methylethyl)phenyl- guanidina hydrochlorida	N-[4-(1-Methylethyl)phenyl]-4-(3- pyridinyl)-2-pyrimidinamino	124-125	
	210	Ex. 30	l-Ethylphenylguanidine hydrochloride	N-(3-Ethylphenyl)-4-(3-pyridinyl)- 2-pyrimidinamine	80-88	
	211	Ex. 11	1-Ethylphenylguanidine hydrochloride	N-(3-Ethylphenyl)-4-(2-pyridinyl)- 2-pyrimidinamine	101-104	
	212	Ex. 11	<pre>3-Benzenesulfonamido- guanidine hydrochloride</pre>	<pre>3-[{4-(2-Pyridinyl)-2-pyrimidinyl}- amino]benzenesulfonamide</pre>	223-225	
	213	Ex. 30	3-Benzenesulfonamido- guanidine hydrochloride	<pre>3-[{4-(3-Pyridinyl)-2-pyrimidinyl}- amino]benzenesulfonamide</pre>	278-280	
	214	Ex. 24	4-(1,1-Dimethylethyl)- phenylguanidine hydro- chlorido	N-{4-(1,1-Dimethylethyl)phenyl]-4- (2-thienyl)-2-pyrimidinamine	150-154	
	215	Ex. 10	4-(Diethylamino)phenyl- guanidine hydrochloride	N.M-Diethyl-W'-[4-(2-furanyl)-2- pyrimidinyl]-1,4-benzenediamine	132-133	

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	МР ^О С
912	Ex. 13	4-Benzenesulfonamido- guanidine hydrochloride	3-[[4-(4-Pyridinyl)-2-pyrimidinyl]- amino]benzenesulfonamide	262-264
217	Ex. 13	4-Acetylaminophenyl- guanidine hydrochloride	N-[3-[[4-(4-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]acetamide	267-270
218	Ек. 30	4-Acetylaminophenyl- guanidine hydrochloride	N-[3-[[4-(3-Pyridinyl)-2-pyrimi- dinyl]amino]phonyl]acetamide	239-241
219	Ex. 11	<pre>3-Acetylaminophenyl- guanidine hydrochloride</pre>	M-[3-[[4-(2-Pyridinyl)-2-pyrimi- dinyl]amino]phenyl]acetamide	190-192
220	Ex. 13	3-(1H-Imidazol-1-yl)- phenylguanidine di- hydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4- (4-pyridinyl)-2-pyrimidinamine	232-234
221	Ex. 13	4-Acetylamino-3-methyl- phenylguanidine hydro- chloride	N-[2-Methyl-4-[[4-(4-pyridinyl)-2- pyrimidinyl]amino]phenyl]acetamide	230-235
222	Ex. 21	4-Acetylaminophenyl- guanidine hydrochloride	N-[4-[[4-(5-Methyl-2-thlenyl)-2- pyrimidinyl]amino]phenyl]acetamide	227-230

TABLE IV (continued)

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×	Acry lophenone Source	Phenylguanidine Precursor	Product	O M M
229	Ex. 13	4-(Imidazol-1-yl)-3- (trifluoromethyl)phen- ylguanidine dihydro- chloride	N-[4-(1 <u>H</u> -Imidazol-1-yl)-3-(trl- fluoromethyl)phenyl]-4-(4-pyridin- yl)-2-pyrimidinamine	238-239
230	Ex. 11	4-Acetylamino-1-methyl- phonylguanidine hydro- chloride	N-[2-Methyl-4-[[4-(2-pyridinyl)-2- pyrimidinyl]amino]phenyl]acetamide	232-234
231	Ex. 30	<pre>3-(1-Imidazolyl)phenyl- guanidine dihydro- chloride</pre>	N-{3-(1H-Imidazol-1-yl)phenyl]-4- (3-pyridinyl)-2-pyrimidinamine	137-144
232	Ex. 24	<pre>3-(1-Imidazolyl)phenyl- guanidine dihydxo- chloride</pre>	N-{3-(111-Imidazolyl)phenyl]-4-(2- thienyl)-2-pyrimidinamine	183-184.5
233	Ex. 10	<pre>J-(1-Imidazolyl)phenyl- guanidine dihydro- chloride</pre>	4-(2-Furanyl)-N-(3-(111-imidazol-1- yl)phenyl)-2-pyrimidinamine	160-168

TABLE IV (continued)

EX.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
234	Ex. 10	<pre>1-(Diethylamino)ethoxy- phenylguanidine dihydro- chloride</pre>	1-(Diethylamino)ethoxy- N-[3-[2-(Diethylamino)ethoxy)phen- phenylguanidine dihydro- ylj-4-(2-furanyl)-2-pyrimidinamine chloride	
235	Ex. 10	3-Methylphenylguanidine hydrochloride	4-(2-Furanyl)-N-(3-methylphenyl)-2- pyrimidinamine, hydrochloride	195-199
236	. Ex. 1.1	4-(1-Imidazolyl)-3-(tri- fluoromethyl)phenyl- guanidine dihydro- chloride	4-(1-Imidazolyl)-3-(trí- N-[4-(lli-Imidazol-1-yl)-3-(trí- fluoromethyl)phenyl)-4-(2-pyridín- yl)-2-pyrimidínamine chloride	216-218
237	Ex. 24	<pre>3-(Diethylamino) athoxy- phenylguanidine di- hydrochloride</pre>	N-[3-[2-(Diethylamino)ethoxy]phen- yl]-4-(2-thienyl)-2-pyrimidinamine	
238	Ек. 10	4-Benzenesulfonamido- guanidine hydrochloride	4-{[4-(2-Furany])-2-pyrimidiny]]- amino]benzenesulfonamide	255-257
239	Ex. 21	4-Benzenesulfonamido- guanidine hydrochloride	4-[[4-(5-Methyl-2-thlenyl)-2- pyrimidinyl]amino]benzenesul- fonamide	241-245

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EX.	Acry Lophenona Source	Phenylguanidine Precursor	Product	нрос
240	Ек. 17	[4-(acetylmethylamino) phenyl]-guanidine hydrochloride	N-Methyl-W-[4-[[4-(3-thlenyl)-2- pyrimidinyl]amino]phenyl]acetamide	150-153
241	Ек. 13	3-[4-Methyl-1-pipera- zinyl]phenylguanidine hydrochloride	N-[3-(4-Methyl-l-piperazinyl)phen- yl]-4-(4-pyrldinyl)-2-pyrlmidina- mine	150-151.5
242	Ex. 10	3-[4-Methyl-1-pipera- zinyl]phenylguanidine hydrochloride	4-(2-Furanyl)-N-[3-(4-methyl-1- piperazinyl)phenyl]-2-pyrimidina- mine	134.5-136
243	Ex. 24	3-[4-Methyl-1-pipera- zinyl)phenylguanidine hydrochloride	N-[3-(4-Methyl-1-piperazinyl)phen- yl]-4-(2-thlenyl)-2-pyrimidinamine	125-126.5
244	Бк. 13	2-Dimethylaminophenyl- guanidine dihydro- chloride	N, N-Dimethyl-N'-(4-(4-pyridinyl)-2- pyrimidinyl)-l,2-benzenedlamine	114-119

TABLE IV (continued)

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Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP ^O C
245	Ex. 13	<pre>3-(Dlethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-[3-[2-(Diethylamino)ethoxy]phen- yl]-4-(4-pyridinyl)-2-pyrimidina- mine	100-103
246	Ex. 24	<pre>J-(Diethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-[4-[2-(Diethylamino)ethoxy]phen- yl]-4-(2-thienyl)-2-pyrimidinamine	
247	Ex. 24	<pre>3-(Dimethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-[4-[2-(Dimethylamino)ethoxy]phen- yl]-4-(2-thienyl)-2-pyrimidinamine	86-96
248	Ex. 17	<pre>3-(Dimethylamino)ethoxy- phenylguanidine di- hydrochloride</pre>	N-[4-[2-(Dimethylamino)ethoxy]phen- yl]-4-(3-thienyl)-2-pyrimidinamine	83-85
249	Ex. 21	4-Diethylaminophenyl- guanidine hydrochloride	N,N-Diethyl-N'-[4-(5-methyl-2-fur- anyl)-2-pyrimidinyl]-1,4-benzene- diamine	118-119
250	. Ex. 21	3-Methoxyphenylguani- dine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2- furanyl)-2-pyrimidinamine	
251	Ex. 13	3-(lH-Imidu zol-l-y l)- phenylguanidine di- hydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4- -(4-pyridinyl)-2-pyrimidinamine	232-239

Example 252

1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone, oxime

[0057] A 2.03 mg portion of N-(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was mixed with 210 ml of absolute ethanol and 1.26 g of hydroxylamine hydrochloride. An 18.2 ml portion of 1N sodium hydroxide was added, the mixture was heated at reflux for 2 hours and then evaporated to 1/4 volume. This was cooled, the solid collected, washed with ethanol and water and dried, giving 1.9 g of the desired product as cream colored crystals, mp 239-241°C.

10 Example 253

1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone, O-methyloxime

[0058] The procedure of Example 252 was repeated using methoxyamine hydrochloride, giving 1.78 g of the desired product as yellow crystals, mp 163-167°C.

Example 254

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N-[1-[4-[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethyl]formamide

[0059] A mixture of 7.25 g of \underline{N} -(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, 100 ml of formamide and 31 ml of 98% formic acid was refluxed with stirring overnight. The solvents were then boiled off for 1/2 hour, the reaction cooled and poured into one liter of water. This was extracted with 725 ml of chloroform. The chloroform extract was back washed with 150 ml of water, then dried, filtered and evaporated to a foam. The foam was partitioned between chloroform and water. An equal volume of saturated potassium bicarbonate was added. The organic phase was separated, dried, filtered and evaporated to a foam. This foam was chromatographed on silica gel topped with a thin layer of hydrous magnesium silicate and eluted with chloroform (first four fractions), then with 2% methanol in chloroform (last two fractions). The sixth (final) fraction was evaporated and then crystallized from chloroform-hexane, giving 1.05 g of the desired product as cream colored crystals, mp 118-121°C.

Example 255

<u>N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine</u>

[0060] A 1.10 g portion of dry 4-[[4(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 25 ml of dimethylformamide. A 213 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A 480 mg portion of 2-dimethylaminoethyl chloride in 2 ml of dimethylformamide was added and the sealed mixture was stirred overnight. The solvent was removed at 60°C and the residue partitioned between 25 ml of water and 50 ml of ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The organic phases were combined, washed with 1N sodium hydroxide, dried, filtered and evaporated. The residue was taken up in 20 ml of chloroform, boiled down to 1/3 volume and hexane added to turbidity. The mixture was allowed to stand overnight, giving 400 mg of the desired product as beige crystals, mp 108-110°C.

Example 256

N-[4-[3-(Dimethylamino)propoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

[0061] A 5.46 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with 3-dimethylaminopropyl chloride by the procedure of Example 255, giving 2.9 g of the desired product, mp 85-87°C.

Example 257

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

[0062] The procedure of Example 256 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 300 mg of the desired product as yellow crystals, mp 85-87°C.

Example 258

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

5 [0063] The procedured of Example 255 was repeated, using 2-diethylaminoethyl chloride, giving 3.45 g of the desired product as yellow crystals, mp 87-89°C.

Example 259

10 N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

[0064] The procedure of Example 255 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 1.6 g of the desired product as yellow crystals, mp 120-122°C.

15 Example 260

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-N',N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine

[0065] The procedure of Example 259 was repeated. Subsequent crops of crystals gave 0.4 g of the desired product, mp 87-91°C.

Example 261

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N-[4-[3-(Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

[0066] A 2.78 g portion of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol and 2.35 g of 3-dimethylaminopropyl chloride were reacted as described in Example 255, giving 850 mg of the desired product, mp 123-124.5°C.

Example 262

[4-[[4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid, ethyl ester

[0067] A mixture of 5.58 g of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with ethyl bromo acetate as described in Example 255, giving 1.8 g of the desired product as yellow crystals, mp 109-111°C.

Example 263

N-(4-Methoxyphenyl)-N-methyl-4-(3-pyridinyl)-2-pyrimidinamine

40 [0068] A 2.78 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 30 ml of dimeth-ylformamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction sealed and stirred for 45 minutes. A solution of 1.70 g of methyl iodide in 2 ml of dimethylformamide was added, the sealed mixture was stirred overnight and the solvent removed. The residue was partitioned between water and chloroform. The organic phase was dried, filtered and evaporated. The residue was crystallized from ether-hexane giving 1.4 g of the desired product as yellow crystals, mp 88-90°C.

Example 264

N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridinyl)-2-pyrimidinamine

[0069] The procedure of Example 263 was repeated using N-(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 510 mg of the desired product as yellow crystals, mp 124-126°C.

Example 265

N-[2-(Diethylamino)ethyl]-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide

[0070] A 1.55 ml portion of diethylenediamine was added to a solution of 0.01 mole of 4-[[4-(3-pyridinyl)-2-py-

rimidinyl]amino]benzoic acid chloride in 50 ml of 1,2-dimethoxyethane. A 10 ml portion of triethylamine was added and the mixture was stirred for 2 hours. The solid was collected, washed with water and recrystallized from absolute ethanol, giving 1.22 g of the desired product, mp 148-150°C.

Example 266

N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide

[0071] A 5.85 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid in 30 ml of thionyl chloride was refluxed on a steam bath for one hour, then evaporated to dryness. The residue was boiled with dimethoxyethane, then cooled and the solid recovered and washed with ether, giving 6.90 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid chloride.

[0072] A 6.03 g portion of the above acid chloride was suspended in 25 ml of ethanol and 10 ml of 25% aqueous methyl amine was added. The resulting solid was collected, taken up in hot 2-methoxyethanol, cooled and the solid collected, giving 3.35 g of the desired product, mp 254-257°C.

Example 267

4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid

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[0073] To a solution of 19.89 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester in 200 ml of 3A ethanol was added 12.5 ml of 10N sodium hydroxide. This mixture was refluxed on a steam bath for 3 hours and then allowed to evaporate. The residue was taken up in water and treated with 10.4 ml of concentrated hydrochloric acid. The resulting solid was collected and dried, giving 18.11 g of the desired product, mp 311-317°C.

Example 268

[4-{[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid

[0074] An 800 mg portion of [4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid, ethyl ester was dissolved in 100 ml of ethanol and 10.7 ml of 1N sodium hydroxide was added. The mixture was stirred for 2 hours, the solvent removed and the residue dissolved in 5 ml of water. The pH was adjusted to 7.0 with 1N hydrochloric acid and the solid collected, washed with water and dried. The solid was recrystallized from dimethylformamideethanol, giving 600 mg of the desired product as yellow crystals, mp 308-310°C.

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Example 269

4-[2-[[4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium iodide

[0075] A 2.0 g portion of N-(4-methoxyphenyl)-4-(4-pyridinyl-2-pyrimidinamine was dissolved in 550 ml of absolute ethanol and filtered. To this was added 10 ml of iodomethane. The reaction was heated on a steam bath for 4 hours. Another 10 ml of iodomethane was added and refluxing was continued overnight. The mixture was cooled, the solid collected, washed with ethanol and dried, giving 2.2 g of the desired product as purple crystals, mp 282-284°C.

45 Example 270

4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

[0076] A 25.0 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 200 ml of 48% hydrobromic acid and stirred overnight under an argon atmosphere. The mixture was then heated on a steam bath for 7 hours, cooled overnight and evaporated at 60°C. The residue was basified with 200 ml of saturated potassium bicarbonate solution and stirred for 1.5 hours. The solid was collected, washed with water, dried and recrystallized from hot absolute ethanol, giving 19.1 g of the desired product, mp 223-225°C.

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Example 271

4-[[4-(4-Pyridinyl)-2-primidinyl]amino]phenol

[0077] The procedure of Example 270 was repeated using N-(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 3.0 g of the desired product as yellow crystals, mp 268-270°C.

Example 272

10 N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

[0078] A 2.73 g portion of dry 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 50 ml of dry dimethyl-formamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A solution of 1.33 g of allyl bromide in 10 ml of dimethylformamide was added, the sealed mixture was stirred overnight and then evaporated at 80°C. The residue was partitioned between water and chloroform. The organic phase was separated, dried and filtered. The filtrate was evaporated and the residue crystallized from chloroform-hexane, giving 1.7 g of the desired product as yellow crystals, mp 105-108°C.

Example 273

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N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, pyridine-1-oxide

[0079] A mixture of 2.76 g of $\underline{\mathbf{N}}$ -(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine and 3.45 g of $\underline{\mathbf{m}}$ -chloroperbenzoic acid in 100 ml of dichloromethane was stirred at room temperature for 20 hours. The mixture was washed three times with an aqueous saturated solution of sodium bicarbonate and a small amount of saturated saline. The organic layer was dried over magnesium sulfate, filtered through diatomaceous earth, then evaporated $\underline{\mathbf{m}}$ vacuo to give a gelatenous solid. The solid was slurried with 50 ml of dichloromethane and filtered. The solid was washed with a small amount of dichloromethane and air dried to give 500 mg of the product. Recrystallization from absolute methanol gave 460 mg of the desired product, mp 223-225°C.

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Example 274

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride

[0080] A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 70 ml of dichloromethane with warming. The solution was cooled to room temperature, then hydrogen chloride gas was bubbled in to give a brick red precipitate. The mixture became very thick and more dichloromethane was added. The precipitate was collected, air dried, then dried in vacuo and gave 2.63 g of the desired product as red-orange crystals, mp 259-262°C.

40 Example 275

N-[4-(4-Pyridinyl-2-pyrimidinyl]-1,4-benzenediamine, hydrochloride

[0081] A 2.85 g amount of N-[4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide was added to a mixture of 10 ml of concentrated hydrochloric acid and 10 ml of water. The reaction mixture was heated at reflux for 90 minutes, then evaporated in vacuo to obtain a solid. The solid was recrystallized from 3A ethanol/water and gave 2.31 g of the desired product as a yellow crystalline solid, mp 292-295°C.

[0082] Additional hydrochloride salts listed in Examples 276 to 287 in Table V were obtained from the corresponding base compound by following procedures similar to those described in Examples 274 and 275 and employing various other solvents such as isopropyl alcohol, ethanol, ether and the like.

TABLE V

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Ex	Compound	MP°C
276	4-(3-Pyridinyl)-N-[3-trifluoromethyl)phenyl]pyrimidinamine, hydrochloride	220-223
277	N.N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	239-245
278	N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	115-150 (dec)

TABLE V (continued)

Ex	Compound	MP°C
279	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-(pyrimidinyl)]-1,3-benzenediamine, dihydrochloride	204-213
280	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, trihydrochloride	202-205
281	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	178-184
282	N-N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	229-234
283	N,N-Dimethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	232-235
284	N-[4-(1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	;
285	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine, hydrochloride	232.5-234
286	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine, hydrochloride	259-266
287	4-(2-Furanyl)-N-[3-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine, hydrochloride	259-263

15 Example 288

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N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate

[0083] A 2.48 g amount of \underline{N} -phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 120 ml of absolute ethanol with heating, then a solution of 1.02 g of concentrated sulfuric acid in 25 ml of ethanol was added dropwise with stirring. The mixture turned orange then a yellow precipitate formed. The mixture was chilled, the precipitate was collected, by filtration, washed with cold ethanol then with ether, and air dried to give 2.73 g of yellow-orange crystals.

[0084] The preceding compound was dissolved in a small amount of water, then a saturated aqueous solution of sodium bicarbonate was added to pH 8.0 to yield a light yellow precipitate. The precipitate was collected, washed with water and dried <u>in vacuo</u>. A 2.25 g portion this material was recrystallized from about 200 ml of absolute methanol in the cold. The product was collected, washed with absolute ethanol and dried <u>in vacuo</u> to give 1.75 g of the desired product as orange cyrstals, mp 233-235°C.

[0085] Additional sulfate salts which were prepared from the corresponding base compound in the manner described hereinabove are listed as Examples 289 to 300 in Table VI.

TABLE VI

Ex	Compound	MP°C
289	4-(2-Pyridinyl)-N-[3-trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	208-211
290	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine, sulfate	207.5-210
291	4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine sulfate	187-193
292	4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl)]-2-pyrimidinamine, sulfate	250-253
293	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	103-123
294	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	167-187
295	4-(3-Pyridinyl)-N-[3-trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	196-199
296	N-(3,5-Dimethylphenyl)-[4-(3-pyridinyl)-2-pyrimidinamine, sulfate	209-214
297	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	216-218
298	N-(3,5-Dimethylphenyl)-4-methyl-6-(5-methyl-2-thienyl)-2-pyrimidinamine, sulfate	232-234
299	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	140-144
300	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, sulfate	204-211

Example 301

50 <u>N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate</u>

[0086] A 2.0 g amount of \underline{N} -phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 2.07 g of phosphoric acid in 25 ml of ethanol was added with stirring. The mixture was chilled for several hours, then the precipitate which formed was collected by filtration, washed twice with cold ethanol and dried $\underline{\text{in vacuo}}$ for 16 hours to give 3.43 g of the desired product as orange crystals, mp 210.5-212.5°C.

[0087] Additional phosphate salts which were prepared from the corresponding base compound in the manner described hereinabove are listed as Examples 302 to 305 in Table VII.

TABLE VII

Ex	Compound	MP°C
302	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	190-192
303	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	185-188
304	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine phosphate	176-179
305	\underline{N} -(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	199-202

10 Example 306

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N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)

[0088] A mixture of 4.97 g of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 2.55 g of maleic acid was dissolved in hot 2-methoxyethanol. Cooling gave 4.15 g of the desired product as an orange crystalline solid, mp 211-214°C.

Example 307

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate

[0089] A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 1.5 ml of concentrated nitric acid in 25 ml of ethanol was added with stirring to give a red-orange precipitate. The mixture was allowed to stand 30 minutes at room temperature, then was chilled for several hours. The solid was collected, washed with cold absolute ethanol and air dried to give 2.80 g of the desired product as red-orange crystals, mp 167-169°C (dec.).

Example 308

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

[0090] A mixture of 4.97 g of \underline{N} -phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 4.62 g of citric acid was dissolved in hot absolute ethanol. Cooling gave 6.14 g of the product of the example as a yellow cystalline solid, mp 155-157°C.

Example 309

Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]amino]acetic acid, ethyl ester

[0091] A 4.08 g portion of 2-phenylamino-4-(4-pyridinyl)pyrimidine was dissolved in 20 ml of dimethylformamide. A 5 g portion of 50% sodium hydride in oil was added using 10 ml of dimethylformamide as a wash. When bubbling ceased, a solution of 2.23 ml of ethyl oxalyl chloride in 10 ml of dimethylformamide was added dropwise. Chloroform and aqueous 10% potassium bicarbonate were added. The organic layer was separated, dried, filtered and evaporated giving the desired product.

Example 310

N-(4-(2-Pyridinyl-2-pyrimidinyl]-4-benzenediamine, dihydrochloride

[0092] A 12.86 g portion of N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide in a mixture of 40 ml of water and 40 ml of concentrated hydrochloric acid was refluxed for 30 minutes and then cooled. The solid was collected and dried, giving 10.84 g of the desired product, mp 285-288 $^{\circ}$ C.

[0093] Following the procedure of this Example, and using as starting materials the products of the indicated examples, the products or Examples 311-322 in Table VIII were derived.

TABLE VIII

Ex.	Starting Material	Product	MP°C
311	Ex. 185	N-Methyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	164-166

TABLE VIII (continued)

	Ex.	Starting Material	Product	MP°C
	312	Ex. 187	N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	110-112
5	313	Ex. 218	N-[4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	279-284
	314	Ex.217	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	199-202
	315	Ex. 221	2-Methyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	297-304
	316	Ex. 219	N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	153-156
10	317	Ex. 182	N-[3-(1-Aminomethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	230(dec.)
	318	Ex. 222	N-[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	284-287
	319	Ex. 228	N-[4-(2-Furanyl)-2-pyrimidinyl]-14-benzenediamine, dihydrochloride	261-266
15	320	Ex. 226	2-Methyl-N-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	176-178
10	321	Ex. 230	2-Methyl-N-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	196-198
	322	Ex. 191	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	192-193.5

Example 323

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2-[1-[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethylidene]hydrazinecarboxamide

[0094] A 2.9 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was mixed with 1.23 g of semi-carbazide hydrochloride in 200 ml of absolute ethanol and 1.10 ml of 10N sodium hydroxide was added. This mixture was refluxed overnight, then cooled to room temperature and the solid collected and washed with ethanol, water and ethanol. The solid was recrystallized from dimethylsulfoxide/ethanol, giving 2.9 g of the desired product, mp 256-258°C.

Example 324

30 N-[4-[2-[bis(1-Methylethyl)amino]ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

[0095] A 2.64 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 60 ml of dimethylformamide by warming on a steam bath and then cooled. A 2.0 g portion of diisopropylaminoethyl chloride hydrochloride was added and dissolved with stirring. A 20 ml portion of 5N sodium hydroxide was added dropwise over 5 minutes, then 5 ml of water was added and the mixture was stirred for 20 hours. The mixture was then heated on a steam bath for 30 minutes, allowed to stand 48 hours and then evaporated. The residual gum was purified by flash dry column chromatography on silica gel eluting fractions 1-3 with methanol and fractions 4-6 with 1% methanol in chloroform. Fractions 4-6 were combined and evaporated, giving 500 mg of the desired product.

40 Example 325

α-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenemethanol

[0096] A 1.45 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was dissolved with stirring in 220 ml of ethanol. A 125 mg portion of sodium borohydride was added and stirring continued for 3 hours. A 63 mg portion of sodium borohydride was added and stirring continued overnight. A 2 ml portion of glacial acetic acid was added and the mixture evaporated. The solid was triturated with water, dried and recrystallized from 30 ml of ethanol giving 710 mg of the desired product, mp 145-147°C.

Example 326

N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethyl]formamide

[0097] A mixture of 2.9 g of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone, 40 ml of formamide and 13 ml of concentrated formic acid was refluxed for 15 hours, then cooled and evaporated. The residue was partitioned between unsaturated aqueous potassium bicarbonate and chloroform. The organic phase was separated, dried, filtered and evaporated. The residue was chormatographed on silica gel, eluting 125 ml fractions, fractions 1-4 with chloroform

and fractions 5-7 with 2% methanol in chloroform. Fractions 5-7 were combined and evaporated, giving 1.25 g of the desired product as a yellow foam.

Example 327

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2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

[0098] A mixture of 35 g of N-(2-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine in 200 ml of 47% aqueous hydrobromic acid was refluxed for 7 hours and then evaporated. The residue was mixed with saturated aqueous potassium bicarbonate and allowed to stand overnight, then filtered. The filtrate was concentrated, giving 3.5 g of the desired compound, mp 166-169°C.

Example 328

N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine

[0099] A solution of 250 ml of 2-acetylpyridine and 500 ml of $\underline{N},\underline{N}$ -dimethylformamide dimethyl acetal was heated on a steam bath for 6 hours. After concentrating the reaction solution under vacuum, 1 liter of hexane was added to the part crystalline residue. The product was collected as small crystalline particles which were washed with an additional liter of hexane. Air drying was followed by drying at 45°C under vacuum, leaving 350.7 g of 3-dimethylamino-1-(2-pyridinyl)-2-propen-1-one.

[0100] A mixture of 289.0 g of imidazole, 292 g of potassium carbonate, 3 liters of dimethyl sulfoxide, and 300.0 g of 1-fluoro-3-nitrobenzene was stirred and heated for 25.5 hours between 105-110°C. Then the reaction was poured into 6 liters of water and cooled in the refrigerator over the weekend. The crystalline product was collected and washed with 1 liter of water. Air drying gave 357.6 g of solid. The solid was taken up in 2.4 liters of ethyl acetate and the hot solution passed through hydrous magnesium silicate. After boiling the filtrate down to 1.5 liters, it was cooled to give a precipitate which was collected and washed with 200 ml of ethylacetate, to leave 151.7 g of off-white crystals. After evaporating the mother liquor to dryness, the residue was recrystallized from 350 ml of ethyl acetate to give 59.7 g more product. The mother liquor from the second fraction was evaporated and the residual material recrystallized twice from ethyl acetate to give 30.9 g more product. Total product, 242.3 g of 1-(3-nitrophenyl)-1H-imidazole.

[0101] In a Parr hydrogenation bottle was placed 75.00 g of 1-(3-nitrophenyl)-1H-imidazole, 0.70 g platinum oxide, and 250 ml of ethanol. Shaking of this mixture in a Parr hydrogenation apparatus was continued until no more hydrogen was taken up. This process was repeated with 76.33 g of the imidazole, 1.0 g of platinum oxide and 250 ml of ethanol and again with 90.4 g of the imidazole, 1.0 g of platinum oxide and 240 ml of ethanol, until a total of 241.63 g had been reduced. For each batch the catalyst was filtered off and the solvent was removed under vacuum; and then the residues were combined to give 207.2 g of gray crystalline amine. Next the amine was recrystallized from 530 ml of 2-propanol. After collecting the product, it was washed with 200 ml of 2-propanol, and dried, under vacuum, to give 156.4 g of 3-(1H-imidazol-1-yl)benzamine.

[0102] A solution of 43.3 g of hydrogen chloride in 290 ml of ethanol was added to 189.0 g of 3-(1<u>H</u>-imidazol-1-yl) benzamine in a 2 liter Erlenmeyer flask. Then 104.7 g of cyanamid was added. The mixture was cautiously warmed in a water bath to an internal temperature of 83°C over 25 minutes. When no exotherm had been noted, the flask was placed inside the steam bath and heated for 2 hours. A final temperature of 97°C was achieved. The resulting brown syrup which was [3-(1<u>H</u>-imidazol-1-yl)phenyl]guanidine, monohydrochloride, was used in the next reaction without further purification.

[0103] A mixture of 164 g of potassium carbonate, 209.1 g of 3-dimethylamino-1-(2-pyridyl)-2-propen-1-one, 1.187 mole of crude [3-(1H-imidazol- 1-yl)phenyl]guanidine monohydrochloride, and 1 liter of methoxyethanol was stirred and heated under very gentle reflux. A dry-ice condenser filled with water was used to prevent plugging by the dimethylammonium carbonate which is given off by the reaction. The reaction was stopped after 26.5 hours and permitted to stand overnight. A heavy precipitate had formed which was collected as A and washed with 100 ml of ether. The filtrate was concentrated under vacuum as B. Both A and B were triturated with 1.5 liters of water. Then A was washed with 300-400 ml of ethanol, followed by 100 ml of ether to leave, on drying, 172.9 g of gray solid, mp 200-202°C. Recrystallization of B from 150 ml of 2-propanol gave a black solid, C. Next, a classical fractional recrystallization was carried out using methoxyethanol as the solvent. In the final stages, a large amount of charcoal was added to remove color. In this fashion two main fractions were obtained D, 79.0 g of yellow crystals, mp 204.5-205.5°C, and E, 18.05 g of yellow crystals, mp 204-204.5°C. The yield of D plus E was 26% of the desired product.

EXAMPLE 329

1-(2-Chloroethoxy)-3-nitrobenzene

[0104] A mixture of 6.96g. of <u>m</u> - nitrophenol, 100 ml. of 2-butanone, 6.9 g. of potassium carbonate, and 11.74 g. of 2 chloroethyl-tosylate was stirred and heated under reflux for 24 hours. After cooling to room temperature, the salts were filtered off and the filtrate concentrated under vacuum. The residue crystallized on seeding and was recrystallized from carbon tetrachloride to give 8.3 g. of product, m.p. 54.5° - 57° C.

10 EXAMPLE 330

1-[2-(3-Nitrophenoxy)ethyl]-1H-imidazole

[0105] After dissolving 3.74 g. of imidazole in 60 ml. of dry N,N-dimethylformamide, 1.78 g. of 50% sodium hydride in oil was added. When the effervescence had stopped (circa 1 hr.), 7.35 g, of 1-(2-chloroethoxy)-3-nitrobenzene was added. After stirring overnight, the reaction was concentrated under vacuum. Water was added to the residue and the product was extracted into chloroform. The product was extracted out of the chloroform layer with dilute hydrochloric acid. Next, the aqueous acid layer was neutralized with potassium carbonate and the oily product extracted into chloroform. Upon drying the chloroform extract with sodium sulfate, it was concentrated under vacuum to an oil which crystallized on standing. Recrystallization from isopropyl acetate gave 6.12 g. of product as the monohydrate, m.p. 52.5°-55.5° C.

EXAMPLE 331

25 3-[2-(1H-Imidazol-1-yl)ethoxy]benzamine

[0106] Using a Parr hydrogenator, 5.00 g, of 1-[2-(3-nitrophenoxy)ethyl]-1H-imidozole in 100 ml. of ethanol and 0.2 g. of platinum oxide was hydrogenated until the hydrogen uptake stopped. The catalyst was filtered off and the filtrate concentrated under vacuum. Several recrystallizations from isopropyl acetate gave 2.8 g. of amine, m.p. 74°-76.5° C.

EXAMPLE 332

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[3-(2-(1H-Imidazol-1-yl)ethoxy]phenyl]-guanidine Dihydrochloride

35 [0107] To a solution of 1.7 g, of hydrogen chloride in 50 ml. of ethanol was added 4.70 g. of 3-[2-(1H-imidazol-1-yl) ethoxy]benzamine in 10 ml. of ethanol. After concentration under vacuum a foam was obtained which gradually crystallized. Next 1.95 g. of cyanamid and 20 ml. of ethanol were added and the mixture heated cautiously, first in a water bath, then directly in a steam bath for a total of 5 hours. A light brown oily guanidine resulted, which was used without purification.

EXAMPLE 333

3-[2-(4 -Morpholinyl)ethoxy]-benzenamine

[0108] N-[2-Chloroethyl)morpholine hydrochloride, 80 g., was partitioned between 5N sodium hydroxide and methylene chloride. After drying the organic layer over magnesium sulfate, the solvent was removed under reduced pressure to leave 65 g. of free amine.

[0109] To 36.01 g. of m-aminophenol dissolved in 325 ml. of N,N-dimethylformamide, 16.3 g, of 50% sodium hydride in oil was added. The reaction was stirred for 1 hour, until the effervescence stopped; then 57 g. of N-(2-chloroethyl) morpholine, from above, was added. After stirring overnight, the mixture was heated on a steam bath for 1/2 hr., then concentrated under vacuum. The residue was taken up in 300 ml. of 2N hydrochloric acid and washed twice with ether. After basifying with 10N sodium hydroxide, the product was extracted into ether, dried (magnesium sulfate), filtered through hydrous magnesium silicate and evaporated to a brown oil. Distillation gave 34.0 g. of a golden oil, b.p. 165°-180° C./0.45mm.

EXAMPLE 334

[3-[2-(4-Morpholinyl)ethoxy]phenyl]guanidine monohydrochloride

[0110] Prepared from 3-[2-(4-morpholinyl)ethoxy]-benza-mine by the method of Example 332

EXAMPLE 335

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1-(Bromoacetyl)-4-methylpiperazine monohydrochloride

[0111] A solution of 10.0 g, of 1-methyepiperazine in 150 ml of chloroform was cooled in a water bath while 17.3 g, of bromoacetyl chloride in 150 ml, of chloroform was added dropwise, with stirring, over 1/2 hour. A calcium chloride tube protected the reaction from moisture. After stirring overnight, the precipitate was collected and washed with chloroform. The crude product was dried under vacuum at 50° and used as such.

EXAMPLE 336

1-[(4-Aminophenoxy)acetyl]-4-methylpiperazine

20 [0112] Prepared from p-aminophenol and 1-(bromoacetyl)-4-methylpiperazine by the method of Example 333 to give a product of m.p. 71°-73° C.

EXAMPLE 337

1-[[4-[(Aminoiminomethyl)amino]phenoxy]acetyl]-4-methylpiperazine Dihydrochloride

[0113] Prepared from 1-[(4-aminophenoxy)acetyl]-4-methylpiperazine by the method of Example 332.

TABLE IX

Ex.	Acryloyl Source	Phenylguanidine precurser	Product	Mp°C.
338	Ex.11	[3-[2-(1H-Imidazol-1-yl)-ethoxy] phenyl]guanidine dihydrochloride	N-[3-[2-(1H-Imidazol-1-yl)ethoxy] phenyl-4-(2-pyridinyl)- 2-pyrimidinamine	149-151.5
339	Ex. 13	[3-[2-(4-morpholinyl)-ethoxy] phenyl]guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)ethoxy] phenyl]-4-(4-pyridinyl)- 2-pyrimidinamine	179-181
340	Ex. 24	[3-[2-(4-morpholinyl)ethoxy]phenyl] guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)ethoxy] phenyl]-4-(2-thienyl)- 2-pyrimidinamine	134-136
341	Ex. 10	[3-[2-(4-morpholinyl)ethoxy]phenyl] guanidine monohydrochloride	4-[2-furanyl) -N-[3-[2-(4-morpholinyl)ethoxy] phenyl]-2-pyrimidinamine	88-90
342	Ex. 24	1-[[4-[(Aminoiminomethyl)amino] phenoxy]acetyl]-4-methyl piperazine dihydrochloride	1-Methyl-4-[[4-(2-thienyl)- 2-pyrimidinyl]-aminophenoxy] acetylpiperazine	173 175
343	Ex. 24	(4-chlorophenyl) guanidine carbonate	N-(4-chlorophenyl)-4-(2-thienyl)- 2-pyrimidinamine	185-186
344	Ex. 26	(2-[bis(1-methylethyl)amino[ethoxy [guanidine hydrochloride	N-[2-[2-(bis(1-methylethyl) amino] ethoxy]phenyl]-4-(3-pyridinyl)- 2-pyrimidinamine	54-57

^[0114] The disease diabetes mellitus is characterized by metabolic defects in the production and utilization of glucose which results in the failure to maintain appropriate blood sugar levels. The result of this defect is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postpran-

dial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and dietary therapies.

[0115] Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is a result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often occurs in the face of normal, or even elevated, levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin.

[0116] The compounds of the present invention and the pharmacologically active acid-addition salts thereof, effectively lower blood glucose levels when administered orally to genetic strains of hyperglycemic mice which are animal models of type II diabetes. The exact mechanism by which they act is not known and the invention should not be construed as limited to any particular mechanism of action. As effective hypoglycemic agents, these compounds are useful for the treatment of hyperglycemia in type II diabetes.

[0117] The compounds of this invention were tested for hypoglycemic activity according to the following procedure. [0118] Obese mice [C57 Bl/6J (ob/ob)], their lean littermates (ob/± or +/+) and diabetic mice [C57 Bl/Ks (db/db)] and their non-diabetic littermates (db/+ or +/+) were obtained from Jackson Laboratories, Bar Harbor, Maine. Obese mice were 8 weeks of age and diabetic mice were 9 weeks of age at the start of the test.

[0119] The test compounds were dissolved in methanol, mixed with powdered food Purina rodent chow on a weight of compound to weight of chow basis and thoroughly dried.

[0120] Groups of 4 control mice received vehicle (methanol) treated chow.

[0121] Groups of 4 test mice were fed ad libitum for one month and food consumption was measured daily (on week days) by weighing the food bins before and after the addition of fresh chow. Thus a 40 g mouse fed the test compound at a concentration of 0.02% of the diet would receive a dose of 20 mg/kg/day if it ate 4 g of chow per day.

[0122] Blood samples were collected before the first treatment and once at the end of each week of treatment by retro-orbital puncture using the end of each week of treatment by retro-orbital puncture using heparinized capillary tubes. Plasma was separated by centrifugation in a Beckman microfuge for 5 minutes. Plasma glucose concentrations were determined with the Beckman Glucose Analyzer which uses a glucose oxidase method.

[0123] The results of this test on representative compounds of this invention appear in Table X.

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TABLE X

Effect of Test Compounds on Blood Glucose

	Type	Dose	Blood G	lucos	e Leve	Blood Glucose Levels in mg/100ml	1/100ml	
COMPOUND	of Mice	(M/M)	0	2 <u>-</u>	Days	14	21	28
N-(4-methylphenyl)-4-(4- Pyridinyl)-2-pyrimidinamine	qo/qo qo/qo	0.1 0.1 0.025	219 210 209	137	118 223	80 166		
N-(4∴Chlorophenyl)-4-(2- thienyl)-2-pyrimidinanine	qo/qo qo/qo	0.1 0.025	212 220	160	148	134		
N-(4-ethylphenyl) -4-(4- Pyridinyl)-2-pyrimidinamine	qo/qo qo/qo	0.1	216 223	181	·			
4-(2-furanyl)-N-phenyl-2- pyrimidinamine	ob/ob 0.1	0.1	214	166		·		

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5	35	30	25	20	15		10	5	
		Table X Con	Cont'd.						ł
	Туре	Dose	Blood	lucos	Glucose Levels	in	mg/100ml	1	
COMPOUND	of Mice	(M/M)	0	در در	Days	14	21	28	
N-[4-(1,1-Dimethylethyl) phenyl]-4-(4pyridinyl)-2- pyrimidinmine		0.1	208 214 218	114	175 155				<u> </u>
	00/00 00/00 00/00 00/00	0.1 0.1 0.05 0.01	229 225 214 214	110	120 139 163	116 143 138	131 180 181	135 188 162	
	db/db db/db db/db	0.1 0.05 0.01	426 429 431		390 314 335	174 293 407	281 250 400	207 270 199	
N(4-(Dimethylamino)phenvl) -4-(4-pyridinyl)-2- pyrimidinamine	qo/qo	0.1	240	130					
N-{4-{3-(Dimethylamino)propoxy} phenyl)-4-(3-pyridinyl) -2-pyrimidinamine	ob/ob	0.1	215	234					
N/4-[2-(Diethylamino)ethoxylphenyl]-4-(3-pyridinyl)-2-pyrimidinamine	qo/qo	0.1	220	191					

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Table X Cont'd

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GNICOMOD	Type	Dose	Blood	Glucos	Leve	Blood Glucose Levels in mg/100ml	1/100m1		
•	Mice	(W/W)	0	S Da	Days	14	21	28	
N'-[4-(2-Benzofurnay1)-2- Pydmidiny1)-N,N-dimethyl- L,4-benzenediamine	qo/qo qo/qo -	0.1 0.1 0.1	229 202 223	153 147 144					
N-[4-[2-[Dimethylam- Ino]ethoxylphenyl]-4- (4-pyridinyl)-2- pyrimidinamine	0b/0b 0b/0b 0b/0b 0b/0b 0b/0b	0.1 0.1 0.05 0.05	218 228 225 232 230 236	151 144 134	167 148 158 163	128 198 252	155 196 175	140 163 177	
	db/db db/db	0.1 0.05 0.01	369 400 360		410 277 393	403 404 321	328 329 494	222 250 336	
N-[4-(1H-Imidazol-1- yl)phenyl)4-(4-pyri- dinyl)-2-pyrimidin- amine	db/db ob/ob ob/ob ob/ob ob/ob ob/ob	0.1 0.1 0.025 0.1 0.1 0.01	424 219 210 211 222 219 222	128	397 200 105 119 1158	233 148 140 132 159 175			
N, N- Diethyl-N ¹ - (4-Ob/ob (3-pyridinyl)-2-pyrim-ob/ob idinyl)-1, 4-benzene-Ob/ob	qo/qo qo/qo qo/qo	0.1 0.1 0.1	223 210 216	138 163 153					

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5		28					
10		/100m1					
		Levels in mg/l00ml	171		244	116 171 161	185 117 ·
15			159		164	109 147 212	175
20	1	Glucose Days	128	171 167 141	137	125 131 126	134
	Table X Cont'd	Blood	225 208 218	217 223 234	227 215 214	221 221 217 217 224 203 231	218 218 220 423
30	Table	Dose (W/W)	0.1 0.025 0.1	0.1	0.1 0.025 0.1	0.1 0.025 0.01 0.1 0.1	0.1 0.025 0.1 0.1
35							
40		Type of Mice	qo/qo qo/qo qo/qo	ob/ob ob/ob ob/ob	qo/qo qo/qo	00/00 00/00 00/00 00/00 00/00	ob/ob ob/ob db/db
45		QN	N-{4-(111-Imidazol- I-yl)phenyl}-4-(3- pyridinyl)-2-pyrim- idinamine	N-[4-(lH-Imidazol- I-yl)phenyl]-4-(2- pyridinyl)-2-pyrimią- inamine	/1)- <u>N</u> -{4- zol-l-yl) -pyrimidin-	.midazol- yl)-4-(2- 2-pyrimid-	
50		COMPOUND	N-{4-(lil-Imidazol- -yl)phenyl)-4-(3- pyridinyl)-2-pyrim idinamine	N- [4-(lil-Imidazol- I-yl)phenyl]-4-(2- pyridinyl)-2-pyrim inamine	4-(2-Furenyl)-N-[4- (1 <u>H</u> -Imidazol-1-yl) phenyl]-2-pyrimidi amine	N-[4-(lll-Imidazol- I-yl)phenyl]-4-(2- thienyl)-2-pyrimid inamine	·

45 50	35 40	30	25	20		15	10	5	
·									
		Table)	X Cont'd				. [·	7
COMPOUND	Type	Dose	Blood	Glucose Levels Davs	Leve		in mg/100ml		
	Mice	(M/M)	0	5	7	14	21	28	
[[4-(3-Pyridiny])- pyrimidiny])amino)	40/qo		240	122					
	qo/qo qo/qo	000	556 578 578 578	211		,			
(3-Chlorophenyl)-4 4-pyrindinyl)-2- rimidinamine	ob/ob ob/ob ob/ob ob/ob ob/ob	0.1 0.1 0.1 0.025	220 237 216 205 210	127 163 135	157	135 129			,
(3-Ghlorophenyl)- -(3-pyridinyl)-2- rimidinamine	ob/ob ob/ob ob/op	0.1 0.025 0.1	205 221 244	135	205	131			
[4-(4-Methyl-1-perazinyl)phenyl) (3-pyridinyl)-2- rimidinamine	qo/qo	0.1	212	236					
(3-Chlorophenyl)- (2-pyridinyl)-2- rimidinamine	qo/qo	0.1	207	204					

Table X Contid

CNICGMOD	Type	Dose	Blood	6111008	e Leve	Blood Glucose Levels in mg/100ml	/100ml	
	Mice	(M/M)	0	21	7	14	21	2.0
4-(2-furanyl)_N-[4- (4-methyl-1-piper- azinyl)phenyl}-2- pyrimidinamine	ob/ob ob/ob ob/ob	0.1 0.025 0.1	203 210 229	149	179	130		
4-(2-Furnnyl)-N- (3-methoxyphenyl) -2-pyrlmidinamine	ob/ob ob/ob ob/ob ob/ob	000.1	221 239 217 219	132 113 162 209		·		
N- [4-(4-Methyl-l- piperazinyl) phenyl] -4-(2-thienyl)-2- pyrimidinamine	ob/ob	0.1	203	1.88				
N-[4-(4-Methyl- I-piperazinvl)ohenyl] -4-(2-pyridinyl)-2- pyrimidinamine	ob/ob	0.1	204	210				

•							
5		26 202 147	279				
10	100m1	170 152 178	178				
	Blood Glucose Levels in mg/100ml	124 200 192	140	134	·	·	
15	Levels	118 157 130	273	154		·	
20	lucose	n		125 131 117 138	173	154	153
25 1 9	Blood G	204	406	221 233 226 235 235	225	228	228
Table X Cont'd	Dose	0.1 . 0.025 0.01	0.1	0.1 0.1 0.1 0.1 0.025	0.1	0.1	0.1
35							
40	Type of	00/q0 qo/qo	qp/qp	06/00 06/00 06/00 06/00	qo/qo	ob/ob ob/ob mine	qo/qo
45		N-[4-(4-Methyl- I-piperazinyl)phenyl] -4-(4-pyridinyl)-2-	namıne		1	ino) (2- dina	N-[2-[2-[Bis(1-methyl-ob/obethyl)amino]ethoxylphenyl]-4-(3-pyridinyl)-2-pyrimid-
50	COMPOUND	N- [4- (4-1 I-pipera: -4- (4-pyr	pyrımıdıı	į	N-[3-(1H-Imidazol I-yl)phenyl]-4- (3-pyridinyl)-2- pyrimidinamine	M-[4-[2-[Diethylam ethoxy]phenyl]-4- thienyl]-2-pyrimi	N-(2-{2-{Bis(1-methy) amino etho; phenyl}-4-(3- pyridinyl)-2-pyr;

Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A compound selected from the group consisting of those of the formula:

$$\begin{array}{c|c}
R_1 \\
R_4 \\
\hline
R_3
\end{array}$$

wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO $_2$ C $_2$ H $_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl-(C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl-(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfamilamido, N,N-dialkyl(C_1 - C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:

$$-(CH_2)_m-R_7$$
, $-X-(CH_2)_m-R_7$ and $-X-CH_2-C-N$ $N-R_8$

wherein R is alkyl (C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1 - C_3), alkoxy(C_1 - C_3), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1 - C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl(C_1 - C_3), halogen or trifluoromethyl; R_3 is 2-py-

ridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1 - C_3); and R_5 is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof; with the proviso that when R_1 is hydrogen, R_2 is 4-methylphenyl, R_4 is hydrogen and R_5 is methyl then R_3 is other than 2-furanyl.

- 2. The compound according to Claim 1; N-{3-(1H-imidazol-1-yl)phenyl}-4-(4-pyridinyl)-2-pyrimidinamine.
- 3. The compound according to Claim 1; N-{3-(1H-imidazol-1-yl)phenyl}-4-(2-pyridinyl)-2-pyrimidinamine.
- 4. The compound according to Claim 1; N,N-dimethyl-N'-{4-methyl-6-(4-pyridinyl)-2-pyrimidinyl}-1,4-benzenediamine.
- 5. The compound according to Claim 1; N'-{4-(2-furanyl)-5-methyl-2-pyrimidinyl}-N,N-dimethyl-1,4-benzenediamine.
- 6. The compound according to Claim 1; N-{4-(dimethylamino)phenyl}-4-(4-pyridinyl)-2-pyrimidinamine.
- 7. The compound according to Claim 1; 4-(2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine.
 - 8. The compound according to Claim 1; N,N-dimethyl-N'-{4-(4-pyridinyl)-2-pyrimidinyl}-1,3-benzenediamine, sulfate.
 - 9. The compound according to Claim 1; N-{4-{2-(diethylamino)ethoxy}phenyl}-4-(4-pyridinyl)-2-pyrimidinamine.
 - 10. The compound according to Claim 1; 4-(1H-indol-3-yl)-N-phenyl-2-pyrimidinamine.
 - 11. The compound according to Claim 1; N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 30 **12.** The compound according to Claim 1; N,N-dimethyl -N'-(4-(3-pyridinyl)-2-pyrimidinyl}-1,4-benzenediamine, trihydrochloride.
 - 13. The compound according to Claim 1; N-{4-(1H-imidazol-1-yl)phenyl}-4-(3-pyridinyl)-2-pyrimidinamine.
- 35 14. The compound according to Claim 1; N-{4-(4-methyl-1-piperazinyl)phenyl}-4-(3-pyridinyl)-2-pyrimidinamine.
 - 15. The compound according to Claim 1; N-{3-methylphenyl}-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. A composition of matter in dosage unit form comprising from about 5 mg to 1500 mg of a compound of Claim 1 in40 association with a pharmaceutically acceptable carrier.
 - 17. A process for producing a compound of the formula:

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$$\begin{array}{c|c}
R_1 \\
R_5 \\
R_4 \\
\hline
\end{array}$$

$$\begin{array}{c|c}
R_1 \\
N \\
R_2 \\
R_3
\end{array}$$

wherein R₁, R₂, R₃, R₄ and R₅ are as defined in Claim 1, which comprises condensing an alkanoyl-heteroaryl derivative of the formula:

wherein R_3 and R_4 are as hereinafter defined with an N,N-di(lower alkyl) formamide or acetamide di(lower alkyl)-acetal at 50°C - 150°C for 4-24 hours to provide a 3-di(lower alkyl)amino acrylophenone of the formula:

which is then cyclized with a substituted phenylguanidine of the formula:

$$R_1$$
 R_1
 R_2
 R_2

wherein R₁ and R₂ are as hereinbefore defined in an inert orgaic solvent at the reflux temperature for 6-48 hours.

18. A compound according to Claim 1 wherein the compund is:

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- N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine;
- N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine;
- N-(4-Ethylphenyl)-4-(-2-pyrazinyl)-2-pyrimidinamine;
- N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamine;
- N-1-Naphthalenyl)-4-(4-pyridinyl)-2-pyrimidinamine;
- N-1-Naphthalenyl)-4-(2-pyridinyl)-2-pyrimidinamine;
- N-Cyclopentyl)-4-(2-pyridinyl)-2-pyrimidinamine;
- N- (Phenyl)-4-(4-quinolinyl)-2-pyrimidinamine;
- N-(Phenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;
- N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;
- N,N-(Dimethyl-N'-{4-(3-methyl-2-thienyl)-2-pyrimidinyl}-1,4-benzenediamine;
- N-{4-(2-Pyridinyl}-2-pyrimidinyl}-1H-benzimidazol-2-amine;
- N-{4-(2-Furanyl)-2-pyrimidinyl}-1H-benzimidazol-2-amine;
- N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine;
- $N-\{4-(2-Furanyl)-2-pyrimidinyl\}-1\underline{H}-benzimidazol-2-amine;\ or$
- N- (3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine.
- 19. Use of a compound selected from the group consisting of those of the formula:

$$\begin{array}{c|c}
R_1 \\
R_4 \\
\hline
R_3
\end{array}$$

wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO $_2$ C $_2$ H $_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl- (C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl-(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfanilamido, N,N-dialkyl(C_1 - C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:

$$\stackrel{\text{NH}_2}{\underset{\text{-CH-CH}_3}{\text{-CH-CH}_3}}$$
, $\stackrel{\text{O}}{\underset{\text{-NHCH}_2-C-N}{\text{-N}}}$, $\stackrel{\text{R}}{\underset{\text{R}}{\text{-N}}}$

$$-(CH_2)_m-R_7$$
, $-X-(CH_2)_m-R_7$ and $-X-CH_2-C-N$ $N-R_8$

wherein R is alkyl (C_1-C_3) , X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl (C_1-C_3) , alkoxy (C_1-C_3) , chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl (C_1-C_3) , phenyl or monosubstituted phenyl wherein the substitutents are alkyl (C_1-C_3) , halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl (C_1-C_3) ; and R_5 is hydrogen or alkyl (C_1-C_3) ; and the pharmacologically acceptable acid-addition salts thereof;

in the preparation of a medicament for the treatment of asthma, allergic diseases, inflammation or diabetes in

mammals

Claims for the following Contracting States: ES, GR

1. A process for producing a compound of the formula

R₅ N N R₂

wherein R_1 is hydrogen, alkyl(C_1 - C_3), -COCO $_2$ C $_2$ H $_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1 - C_6), alkoxy(C_1 - C_3), chloro, bromo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl(C_1 - C_3)amino, dialkyl(C_1 - C_3)amino, alkyl(C_1 - C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfanilamido, N,N-dialkyl(C_1 - C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formulae:

$$^{\text{NH}_2}_{\text{-CH-CH}_3}$$
, $^{\text{-NHCH}_2}$ - $^{\text{C}}_{\text{-N}}$ R, $^{\text{R}}_{\text{R}}$

$$-(CH_2)m-R_7$$
, $-X-(CH_2)m-R_7$ and $-X-CH_2-C-N$ $N-R_8$

wherein R is alkyl(C_1 - C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1 - C_3), alkoxy (C_1 - C_3), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1 - C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1 - C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 6-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 2-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1 - C_3);

and R_5 is hydrogen or alkyl(C_1 - C_3); and the pharmacologically acceptable acid-addition salts thereof with the proviso that when R_1 is hydrogen, R_2 is 4-methylphenyl, R_4 is hydrogen and R_5 is methyl then R_3 is other than 2-furanyl, said process comprising condensing an alkanoyl-heteroaryl derivative of the formula:

wherein R_3 and R_4 are as hereinbefore defined with an N,N-di(lower alkyl) formamide or acetamide di (lower alkyl)-acetal at 50°-150°C for 4-24 hours to provide a 3-di(lower alkyl)amino acrylophenone of the formula:

which is then cyclized with a substituted phenylguanidine of the formula:

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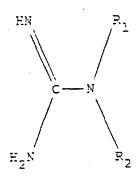
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wherein R_1 and R_2 are as hereinbefore defined in an inert organic solvent at the reflux temperature for 6-48 hours.

- 2. The process according to Claim 1 for producing N-[3-(1H-imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
- 3. The process according to Claim 1 for producing N-[3-(1H-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine.
- The process according to Claim 1 for producing N,N-dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine.
- 5. The process according to Claim 1 for producing N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-ben-zenediamine.
- 6. The process according to Claim 1 for producing N-[4-(dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 7. The process according to Claim 1 for producing 4-(2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine.
 - 8. The process according to Claim 1 for producing N,N-dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-13-benzenediamine, sulfate.
 - 9. The process according to Claim 1 for producing N-[4-[2-(diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

- 10. The process according to Claim 1 for producing 4-(1H-indol-3-yl)-N-phenyl-2-pyrimidinamine.
- 11. The process according to Claim 1 for producing N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- The process according to Claim 1 for producing N,N-dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride.
 - 13. The process according to Claim 1 for producing N-[4-(1H-imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 10 14. The process according to Claim 1 for producing N-[4-(4-methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
 - 15. The process according to Claim 1 for producing N-(3-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 15 16. The process according to Claim 1 for producing the following compounds

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine;

N-(4-Ethylphenyl)-6-methyl-4(6-methyl-3-pyridinyl)-2-pyrimidin-amine;

N-(4-Ethylphenyl)-4(-2-pyrazinyl)-2-pyrimidinamine;

N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamine;

N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine;

N-1-Naphthalenyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

N-Phenyl-4-(4-quinolinyl)-2-primidinamine;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-primidinyl]-1,4-benzenediamine;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amine;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidazol-2-amine;

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine;

Patentansprüche

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Patentansprüche für folgende Vertragsstaaten: AT-BE-CH-DE-FR-GB-IT-LI-NL-SE

1. Verbindung, die aus der Gruppe ausgewählt ist, die aus denjenigen der Formel:

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besteht, in der R_1 Wasserstoff, (C_1-C_3) -Alkyl, $-COCO_2C_2H_5$ oder N,N-Dimethylaminoethyl ist; R_2 mono- oder polysubstituiertes Phenyl ist, worin die Substituenten (C_1-C_6) -Alkyl, (C_1-C_3) -Alkoxy, Chlor, Brom, Trifluormethyl, Hydroxy, Phenyl, Amino, (C_1-C_3) -Monoalkylamino, (C_1-C_3) -Dialkylamino, (C_1-C_3) -Alkylketo, Propenyloxy, Carboxyl, Oxyessigsäure, Oxyessigsäureethylester, Sulfanilamido, N,N- (C_1-C_3) -Dialkylsulfanilamido, N-Methylpiperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethylbenzyl oder Einheiten der Formeln:

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$$^{\mathrm{NH}_2}_{-\mathrm{CH-CH}_3}$$
, $^{\mathrm{NHCH}_2-\mathrm{C-N}}_{-\mathrm{C-N}_R}$, $^{\mathrm{R}}_{-\mathrm{N}}$

$$-(CH_2)m-R_7$$
, $-X-(CH_2)m-R_7$ und $-X-CH_2-C-N$ $N-R_8$

sind, worin R (C_1 - C_3)-Alkyl ist, X Sauerstoff (-O-) oder Schwefel (-S-) ist, m 1 - 3 ist, n 2 oder 3 ist, R_6 Wasserstoff, (C_1 - C_3)-Alkyl, (Phenyl oder monosubstituiertes Phenyl ist, worin die Substituenten (C_1 - C_3)-Alkyl, Halogen oder Trifluormethyl sind; R_3 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Methyl-3-pyridinyl, 6-Methyl-3-pyridinyl, 2-Furanyl, 5-Methyl-2-furanyl, 2,5-Dimethyl-3-furanyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 2-Pyrazinyl, 2-Benzofuranyl, 2-(Pyridin-N-oxid), 3-(Pyridin-N-oxid), 4-(Pyridin-N-oxid), 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Chinolinyl, 4-Pyridinylmethyliodid, Dimethylaminophenyl oder N-Acetyl-N-methylaminophenyl ist; R_4 Wasserstoff oder (C_1 - C_3)-Alkyl ist; und R_5 Wasserstoff oder (C_1 - C_3)-Alkyl 1st; und die pharmakologisch annehmbaren Säureadditionssalze derselben, mit der Maßgabe, dass wenn R_1 für Wasserstoff, R_2 für 4-Methylphenyl, R_4 für Wasserstoff, und R_5 für Methyl steht, dann ist R_3 kein 2-Furanyl.

- Verbindung nach Anspruch 1: N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
- Verbindung nach Anspruch 1: N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamin.
 - 4. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamin.
 - 5. Verbindung nach Anspruch 1: N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzoldiamin.
 - 6. Verbindung nach Anspruch 1: N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
 - 7. Verbindung nach Anspruch 1: 4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamin.
- 50 8. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzoldiaminsulfat.
 - 9. Verbindung nach- Anspruch 1: N-[4-[2-(Diethylamino)-ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.
 - 10. Verbindung nach Anspruch 1: 4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamin.
 - 11. Verbindung nach Anspruch 1: N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.
 - 12. Verbindung nach Anspruch 1: N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamintrihydrochlorid.

- 13. Verbindung nach Anspruch 1: N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
- 14. Verbindung nach Anspruch 1: N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.
- 5 15. Verbindung nach Anspruch 1: N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.
 - 16. Substanz-Zusammensetzung in Einheitsdosierungsform, umfassend ungefähr 5 mg bis ungefähr 1500 mg einer Verbindung nach Anspruch 1 zusammen mit einem pharmazeutisch annehmbaren Träger.
- 10 17. Verfahren zur Herstellung einer Verbindung der Formel:

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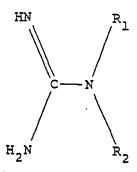
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in der R_1 , R_2 , R_3 , R_4 und R_5 wie in Anspruch 1 definiert sind, umfassend das Kondensieren eines Alkanoylheteroaryl-Derivats der Formel:

in der R₃ und R₄ wie vorstehend definiert sind, mit einem N,N-Di(niederalkyl)formamid oder Acetamiddi(niederalkyl)-acetal über 4 - 24 Stunden bei 50 - 150°C, um ein 3-Di(niederalkyl)aminoacrylophenon der Formel:

$$R_{1}$$
 R_{2} R_{3} R_{3} R_{4} R_{5} R_{3} R_{3} R_{4} R_{5} R_{5} R_{3} R_{5} R_{5

bereitzustellen, das dann mit einem substituierten Phenylquanidin der Formel:



in der $\rm R_1$ und $\rm R_2$ wie vorstehend definiert sind, in einem inerten organischen Lösungsmittel 6 - 48 Stunden bei der Rückflußtemperatur cyclisiert wird.

18. Verbindung nach Anspruch 1, worin die Verbindung ist:

N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

N-(4-Ethylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(4-pyridinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Phenyl-4-(4-chinolinyl)-2-pyrimidinamin;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzoldiamin;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin; oder

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamin.

19. Verwendung einer Verbindung, die aus der Gruppe ausgewählt ist, die aus derjenigen der Formel

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besteht, in der R_1 Wasserstoff, (C_1-C_3) -Alkyl, $-COCO_2C_2H_5$ oder N,N-Dimethylaminoethyl ist; R_2 mono- oder polysubstituiertes Phenyl ist, worin die Substituenten (C_1-C_6) -Alkyl, (C_1-C_3) -Alkoxy, chlor, Brom, Trifluormethyl, Hydroxy, Phenyl, Amino, (C_1-C_3) -Monoalkylamino, (C_1-C_3) -Dialkylamino, (C_1-C_3) -Alkylketo, Propenyloxy, Carboxyl, Oxyessigsäure, Oxyessigsäureethylester, Sulfanilamido, N,N- (C_1-C_3) -Dialkylsulfanilamido, N-Methylpiperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethylbenzyl oder Einheiten der Formeln:

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$$\begin{array}{c} \text{O} \\ \text{II} \\ \text{-C-NH-}(\text{CH}_2) \text{ n-N} \end{array}, \begin{array}{c} \text{R} \\ \text{-CH-CH}_3, \text{-C-CH}_3, \\ \text{-C-CH}_3, \end{array}$$

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$$-CH-CH_3$$
, $-NHCH_2-C-N$, R

$$-(CH_2)m-R_7$$
, $-X-(CH_2)m-R_7$ und $-X-CH_2-C-N-R_8$

sind, worin R (C_1 - C_3)-Alkyl ist, X Sauerstoff (-O-) oder Schwefel (-S-) ist, m 1 - 3 ist, n 2 oder 3 ist, R_6 Wasserstoff, (C_1 - C_3)-Alkyl, (C_1 - C_3)-Alkyl, Chlor, Brom, lod oder Trifluormethyl ist, R_7 1H-Imidazol-1-yl oder Morpholino ist und R_8 (C_1 - C_3)-Alkyl, Phenyl oder monosubstituiertes Phenyl ist, worin die Substituenten (C_1 - C_3)-Alkyl, Halogen oder Trifluormethyl sind; R_3 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Methyl-3-pyridinyl, 6-Methyl-3-pyridinyl, 2-Furanyl, 5-Methyl-2-furanyl, 2,5-Dimethyl-3-furanyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 2-Pyrazinyl, 2-Benzofuranyl, 2-(Pyridin-N-oxid), 3-(Pyridin-N-oxid), 4-(Pyridin-N-oxid), 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Chinolinyl, 4-Pyridinylmethyliodid, Dimethylaminophenyl oder N-Acetyl-N-methylaminophenyl ist; R_4 Wasserstoff oder (C_1 - C_3)-Alkyl ist; und R_5 Wasserstoff oder (C_1 - C_3)-Alkyl ist; und die pharmakologisch annehmbaren Säureadditionssalze derselben, zur Herstellung eines Medikaments zur Behandlung von Asthma, Allerien, Entzündungen und Diabetes bei Säugern.

Patentansprüche für folgende Vertragsstaaten : ES und GR

1. Verfahren zur Herstellung einer Verbindung der Formel:

in der R_1 Wasserstoff, (C_1-C_3) -Alkyl, $-COCO_2C_2H_5$ oder N,N-Dimethylaminoethyl ist; R_2 mono- oder polysubstituiertes Phenyl ist, worin die Substituenten (C_1-C_6) -Alkyl, (C_1-C_3) -Alkoxy, Chlor, Brom, Trifluormethyl, Hydroxy, Phenyl, Amino, (C_1-C_3) -Monoalkylamino1 (C_1-C_3) -Dialkylamino, (C_1-C_3) -Alkylketo, Propenyloxy, Carboxyl, Oxyessigsäure, Oxyessigsäureethylester, Sulfanilamido, N,N- (C_1-C_3) -Dialkylsulfanilamido, N-Methylpiperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethylbenzyl oder Einheiten der Formeln:

$$_{10}^{0}$$
 -C-NH-(CH₂)п-N $_{R}^{0}$, -CH-CH₃, -C-CH₃, -C-CH₃

$$^{NH}_{2}$$
 -CH-CH₃, -NHCH₂-C-N_R, -N R

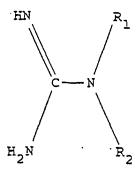
$$-(CH_2)m-R_7$$
, $-X-(CH_2)m-R_7$ und $-X-CH_2-C-N$ $N-R_8$

sind, worin R (C_1 - C_3)-Alkyl ist, X Sauerstroff (-O-) oder Schwefel (-S-) ist, m 1 - 3 ist, n 2 oder 3 ist, R₆ Wasserstoff, (C_1 - C_3)-Alkyl, (C_1 - C_3) -Alkoxy, Chlor, Brom, lod oder Trifluormethyl ist, R₇ 1H-Imidazol-1-yl oder Morpholino ist und R₈ (C_1 - C_3)-Alkyl, Phenyl oder monosubstituiertes Phenyl ist, worin die Substituenten (C_1 - C_3)-Alkyl, Halogen oder Trifluormethyl sind;

 R_3 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Methyl-3-pyridinyl, 6-Methyl-3-pyridinyl, 2-Furanyl, 5-Methyl-2-furanyl, 2,5-Dimethyl-3-furanyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 2-Pyrazinyl, 2-Benzofuranyl, 2-(Pyridin-N-oxid), 3-(Pyridin-N-oxid), 4-(Pyridin-N-oxid), 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Chinolinyl, 4-Pyridinylmethyliodid, Dimethylaminophenyl oder N-Acetyl-N-methylaminophenyl ist; R_4 Wasserstoff oder (C_1 - C_3)-Alkyl ist; und R_5 Wasserstoff oder (C_1 - C_3)-Alkyl ist; und der pharmakologisch annehmbaren Säureadditionssalze derselben, mit der Maßgabe, dass wenn R_1 für Wasserstoff, R_2 für 4-Methylphenyl, R_4 für Wasserstoff, und R_5 für Methyl steht, dann ist R_3 kein 2-Furanyl wobei das Verfahren umfaßt: das Kondensieren eines Alkanoylheteroaryl-Derivats der Formel:

in der R_3 und R_4 wie vorstehend definiert sind, mit einem N,N-Di(niederalkyl)formamid oder Acetamiddi(niederalkyl)-acetal über 4 - 24 Stunden bei 50 - 150°C, um ein 3-Di(niederalkyl)aminoacrylophenon der Formel:

bereitzustellen, das dann mit einem substituierten Phenylguanidin der Formel:



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in der R1 und R2 wie vorstehend definiert sind, in einem inerten organischen Lösungsmittel 6 - 48 Stunden bei der Rückflußtemperatur cyclisiert wird.

Verfahren nach Anspruch 1 zum Herstellen von N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.

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- Verfahren nach Anspruch 1 zum Herstellen von N-[3-(1H-Imidazol-1-yl)phenyl)-4-(2-pyridinyl)-2-pyrimidinamin.
- Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamin.

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- Verfahren nach Anspruch 1 zum Herstellen von N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzoldiamin.
- 6. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.

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7. Verfahren nach Anspruch 1 zum Herstellen von 4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamin.

Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzoldiamin-

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Verfahren nach Anspruch 1 zum Herstellen von N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamin.

10. Verfahren nach Anspruch 1 zum Herstellen von 4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamin.

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11. Verfahren nach Anspruch 1 zum Herstellen von N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.

12. Verfahren nach Anspruch 1 zum Herstellen von N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzoldiamintrihydrochlorid.

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13. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamin.

14. Verfahren nach Anspruch 1 zum Herstellen von N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidi-

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namin.

15. Verfahren nach Anspruch 1 zum Herstellen von N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamin.

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N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;

16. Verfahren nach Anspruch 1, das die folgenden Verbindungen erzeugt:

- N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamin;
- N-(4-Ethylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;
- N-(3-Methylphenyl)-4-(2-pyrazinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(4-pyridinyl)-2-pyrimidinamin;

N-1-Naphthalinyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamin;

N-Phenyl-4-(4-chinolinyl)-2-pyrimidinamin;

N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamin;

N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-3-pyrimidinamin;

N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzoldiamin;

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amin;

N-[4-(2-Furanyl)-2-Pyrimidinyl]-1H-benzimidazol-2-amin;

N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamin.

Revendications

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1. Un composé choisi dans la classe formée par ceux de formule :

où R_1 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , -COCO $_2$ C $_2$ H $_5$ ou N,N-diméthylaminoéthyle ; R_2 est un groupe phényle mono- ou polysubstitué dans lequel les substituants sont des groupes alkyle en C_1 - C_6 , alcoxy en C_1 - C_3 , chloro, bromo, trifluorométhyle, hydroxyle, phényle, amino, mono-(alkyle en C_1 - C_3)amino, di(alkyle en C_1 - C_3)amino, (alkyle en C_1 - C_3)céto, propényloxy, carboxyle, acide oxyacétique, ester éthylique d'acide oxyacétique, sulfanilamido, N,N-di(alkyle en C_1 - C_3)sulfanilamido, N-méthylpipérazinyle, pipéridinyle, 1H-imidazol-1-yle, 1H-benzimidazol-2-yle, 1-naphtyle, cyclopentyle, 3,4-diméthylbenzyle ou des groupements de

où R est un groupe alkyle en C_1 - C_3 , X est un atome d'oxygène (-O-) ou de soufre (-S-), m est de 1 à 3, n est 2 ou 3, R_6 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , alcoxy en C_1 - C_3 , chloro, bromo, iodo ou trifluoromé-

thyle, R_7 est un groupe 1H-imidazol-1-yle ou morpholino et R_8 est un groupe alkyle en C_1 - C_3 , phényle ou phényle monosubstitué dont les substituants sont des groupes alxyle en C_1 - C_3 , halogéno ou trifluorométhyle ; R_3 est un groupe 2-pyridinyle, 3-pyridinyle, 4-pyridinyle, 2-méthyl-3-pyridinyle, 6-méthyl-3-pyridinyle, 2-furanyle, 5-méthyl-2-thiényle, 2-phénothiazinyle, 2-pyrazinyle, 2-benzofuranyle, 2-(N-oxyde de pyridine), 3-(N-oxyde de pyridine), 4-(N-oxyde de pyridine), 1N-indol-3-yle, 1-méthyl-1N-pyrrol-2-yle, 4-quinolyle, iodure de 4-(N-méthyl) pyridinyle diméthylaminophényle ou N-acétyl-N-méthylaminophényle ; R_4 est un atome d'hydrogène ou un groupe alkyle en N-capitale en N

- 2. Le composé selon la revendication 1 : la N-[3-(1H-imidazol-1-yl)phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
- 3. Le composé selon la revendication 1 : la N-[3-(1H-imidazol-1-yl)phényl]-4-(2-pyridinyl)-2-pyrimidinamine.
- 4. Le composé selon la revendication 1 : la N,N-diméthyl-N'-[4-méthyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
- 5. Le composé selon la revendication 1 : la N'-[4-(2-furanyl)-5-méthyl-2-pyrimidinyl]-N,N-diméthyl-1,4-benzènedia-
 - 6. Le composé selon la revendication 1 : la N-[4-(diméthylamino)phényl]-4-(4-pyrinyl)-2-pyrimidinamine.
 - 7. Le composé selon la revendication 1 : la 4-(2-furanyl)-N-(3-méthylphényl)-2-pyrimidinamine.
 - 8. Le composé selon la revendication 1 : le sulfate de *N*,*N*-diméthyl-*N*'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzènediamine.
 - 9. Le composé selon la revendication : la N-[4-[2-(diéthylamino)éthoxy]phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 10. Le composé selon la revendication 1 : la 4-(1H-indol-3-yl)-N-phényl-2-pyrimidinamine.
 - 11. Le composé selon la revendication 1 : la N-(4-éthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 35 12. Le composé selon la revendication 1 : le trichlorhydrate de N,N-diméthyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-ben-zènediamine.
 - 13. Le composé selon la revendication 1 : la N-[4-(1H-imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 40 14. Le compose selon la revendication 1 : la N-[4-(4-méthyl-1-pipérazinyl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.
 - 15. Le composé selon la revendication 1 : la N-(3-méthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. Une composition de matière sous formé d'unité posologique conprenant environ 5 mg à environ 1500 mg d'un composé de la revendication 1 en association avec un support pharmaceutiquement acceptable.
 - 17. un procédé de production d'un composé de la formule :

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où R₁, R₂, R₃, R₄ et R₅ sont tels que définis dans la revendication 1, qui comprend la condensation d'un dérivé alcanoyl-hétéroaryle de formule :

où R₃ et R₄ sont tels que définis ci-dessus, avec un acétal de di(alkyle inférieur) de N,N-di(alkyle inférieur)-formamide ou acétamide entre 50° et 150°C pendant 4 à 24 heures pour produire une 3-di(alkyle inférieur)aminoacrylophénone de formule :

qui est ensuite cyclisée avec une phénylguanidine substituée de formule :

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où R₁ et R₂ sont tels que définis ci-dessus, dans un solvant organique inerte à la température de reflux pendant 6 à 48 heures.

18. Un composé selon la revendication 1, dans lequel le composé est :

la N-(4-éthylphényl)-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;

la N-(4-éthylphényl)-6-méthyl-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;

la N-(4-éthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-1-naphtalényl-4-(4-pyridinyl)-2-pyrimidinamine;

la N-1-naphtalényl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-phényl-4-(4-quinolyl)-2-pyrimidinamine;

la N-phényl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

la N,N-diméthyl-N'-[4-(3-méthyl-2-thiényl)-2-pyrimidinyl]-1,4-benzènediamine;

la N-[4-(2-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole-2-amine;

la N-[4-(2-furanyl)-2-pyrimidinyl]-1H-benzimidazole-2-amine;

la N-(3-méthoxyphényl)-4-(3-méthyl-2-thiényl)-2-pyrimidinamine;

la N-[4-(2-furanyl)-2-pyrimidinyl]-1H-benzimidazole-2-amine; ou

la N-(3-méthoxyphényl)-4-(3-méthyl-2-thienyl)-2-pyrimidinamine.

19. Utilisation d'un composé choisi dans la classe formée par ceux de formule :

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où R_1 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , -COCO $_2$ C $_2$ H $_5$ ou N, N-diméthylmaminoéthyle; R_2 est un groupe phényle mono- ou polysubstitué dans lequel les substituants sont des groupes alkyle en C_1 - C_6 , alcoxy en C_1 - C_3 , chloro, bromo, trifluorométhyle, hydroxyle, phényle, amino, mono-(alkyle en C_1 - C_3)amino, di (alkyle en C_1 - C_3)amino, (alkyle en C_1 - C_3)céto, propényloxy, carboxyle, acide oxyacétique, ester éthylique d'acide oxyacétique, sulfanilamido, N, N-di(alkyle en N-N-di(alkyle en N-N-di(alky

où R est un groupe alkyle en C_1 - C_3 , X est un atome d'oxygène (-O-) ou de soufre (-S-), m est de 1 à 3, n est 2 ou 3, R_6 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , alcoxy en C_1 - C_3 , chloro, bromo, iodo ou trifluorométhyle, R_7 est un groupe 1H-imidazol-1-yle ou morpholino et R_8 est un groupe alkyle en C_1 - C_3 , phényle ou phényle monosubstitué dont les substituants sont des groupes alkyle en C_1 - C_3 , halogéno ou trifluorométhyle ; R_3 est un groupe 2-pyridinyle, 3-pyridinyle, 4-pyridinyle, 2-méthyl-3-pyridinyle, 6-méthyl-3-pyridinyle, 2-furanyle, 5-méthyl-2-furanyle, 2,5-diméthyl-3-furanyle, 2-thiényle, 3-thiényle, 5-méthyl-2-thiényle, 2-phénothiazinyle, 2-pyrazinyle, 2-benzofuranyle, 2-(N-oxyde de pyridine), 3-(N-oxyde de pyridine), 4-(N-oxyde de pyridine)-, 1N-indol-2-yle, 1N-indol-3-yle, 1-méthyl-1N-pyrrol-2-yle, 4-quinolyle, iodure de 4-(N-méthyl) pyridinyle diméthylaminophényle ou N-acétyl-N-méthylaminophényle ; R_4 est un atome d'hydrogène ou un groupe alkyle en N-N-cyle de pyridine) d'acide pharmacologiquement acceptables. Pour la préparation d'un médicament pour le traitement de l'asthme, de diabètes, d'inflammations ou de maladies allergiques, chez un mammifère.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de formule :

où R_1 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , -COCO $_2$ C $_2$ H $_5$ ou N,N-diméthylaminoéthyle , R_2 est un groupe phényle mono- ou polysubstitué dans lequel les substituants sont des groupes alkyle en C_1 - C_6 , alcoxy en C_1 - C_3 , chloro, bromo, trifluorométhyle, hydroxyle, phényle, amino, mono-(alkyle en C_1 - C_3)amino, di(alkyle en C_1 - C_3)amino, (alkyle en C_1 - C_3)céto, propényloxy, carboxyle, acide oxyacétique, ester éthylique d'acide oxyacétique, sulfanilamido, N,N-di(alkyle en C_1 - C_3)sulfanilamido, N-méthylpipérazinyle, pipéridinyle, 1H-imidazol-1-yle, 1H-triazol-1-yl, 1H-benzimidazol-2-yle, 1-naphtyle, cyclopentyle, 3,4-diméthylbenzyle ou des groupements de formule :

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ou R est un groupe alkyle en C_1 - C_3 , X est un atome d'oxygène (-O-) ou de soufre (-S-), m est de 1 à 3, n est 2 ou 3, R_6 est un atome d'hydrogène, un groupe alkyle en C_1 - C_3 , alcoxy en C_1 - C_3 , chloro, bromo, iodo ou trifluorométhyle, R_7 est un groupe 1H-imidazol-1-yle ou morpholino et R_8 est un groupe alkyle en C_1 - C_3 , phényle ou phényle monosubstitué dont les substituants sont des groupes alkyle en C_1 - C_3 , halogéno ou trifluorométhyle ; R_3 est un groupe 2-pyridinyle, 3-pyridinyle, 4-pyridinyle, 2-méthyl-3-pyridinyle, 6-méthyl-3-pyridinyle, 2-furanyle, 5-méthyl-2-thiényle, 2-phénothiazinyle, 2-pyrazinyle, 2-benzofluranyle, 2-(N-oxyde de pyridine), 3-(N-oxyde de pyridine), 4-(N-oxyde de pyridine), 1N-indol-2-yle, 1N-indol-3-yle, 1-méthyl-1N-pyrrol-2-yle, 4-quinolyle, iodure de 4-(N-méthyl) pyridinyle diméthylaminophényle ou N-acétyl-N-méthylaminophényle ; R_4 est un atome d'hydrogène ou un groupe alkyle en N-N-méthylaminophényle en N-N-méthylaminophényle en N-N-méthylaminophényle, alors N-N-méthylaminophényle, N-N-méthylaminoph

où R₃ et R₄ sont tels que définis ci-dessus, avec un acétal de di(alkyle inférieur) de N,N-di(alkyle inférieur)-

formamide ou acétamide entre 50° et 150°C pendant 4 à 24 heures pour produire une 3-di(alkyle inférieur)aminoacrylophénone de formule :

0 R₄ R₅ R₃-C-C-C-N(alkyle inférieur),

qui est ensuite cyclisée avec une phénylguanidine substituée de formule :

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H₂N R

- où R_1 et R_2 sont tels que définis ci-dessus, dans un solvant organique inerte à la température de reflux pendant 6 à 48 heures.
 - 2. Procédé selon la revendication 1 pour la préparation de la N-[3-(1H-imidazol-1-yl)Phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
- Procédé selon la revendication 1 pour la préparation de la N-[3-(1H-imidazol-1-yl)phényl]-4-(2-pyridinyl)-2-pyrimidinamine.
 - 4. Procédé selon la revendication 1 pour la préparation de la N,N-diméthyl-N'-[4-méthyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
 - 5. Procédé selon la revendication 1 pour la préparation de la N'-[4-(2-furanyl)-5-méthyl-2-pyrimidinyl]-N,N-diméthyl-1,4-benzènediamine.
- 6. Procédé selon la revendication 1 pour la préparation de la N-[4-(diméthylamino)phényl]-4-(4-pyridinyl)-2-pyrimidinamine.
 - 7. Procédé selon la revendication 1 pour la préparation de la 4-(2-furanyl)-N-(3-méthylphényl)-2-pyrimidinamine.
- 8. Procédé selon la revendication 1 pour la préparation du sulfate de N,N-diméthyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]1,3-benzènediamine.
 - Procédé selon la revendication 1 pour la préparation de la N-[4-[2-(diéthylamino)éthoxy]phényl]-4-(4-pyridinyl) 2-pyrimidinamine.
- 50 10. Procédé selon la revendication 1 pour la préparation de la 4-(1H-indol-3-yl)-N-phényl-2-pyrimidinamine.
 - 11. Procédé selon la revendication 1 pour la préparation de la N-(4(éthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 12. Procédé selon la revendication 1 pour la préparation du trichlorhydrate de N,N-diméthyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzènediamine.
 - 13. Procédé selon la revendication 1 pour la préparation de la N-[4-(1H-imidazol-1-yl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.

- 14. Procédé selon la revendication 1 pour la préparation de la N-[4-(4-méthyl-1-pipérazinyl)phényl]-4-(3-pyridinyl)-2-pyrimidinamine.
- 15. Procédé selon la revendication 1 pour la préparation de la N-(3-méthylphényl)-4-(4-pyridinyl)-2-pyrimidinamine.
- 16. Procédé selon la revendication 1 pour la préparation des composés suivants :

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la N-(4-éthylphényl)-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;
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la N-(4-éthylphényl)-6-méthyl-4-(6-méthyl-3-pyridinyl)-2-pyrimidinamine;

la N-(4-éthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(2-pyrazinyl)-2-pyrimidinamine;

la N-1-naphtalényl-4-(4-pyridinyl)-2-pyrimidinamine;

la N-1-naphtalényl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine;

la N-phényl-4-(4-quinolyl)-2-pyrimidinamine;

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la N-phényl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

la N-(3-méthylphényl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine;

la N,N-diméthyl-N'-[4-(3-méthyl-2-thiényl)-2-pyrimidinyl]-1,4-benzènediamine ;

la N-[4-(2-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole-2-amine;

la N-[4-(2-furanyl)-2-pyrimidinyl]-1H-benzimidazole2-amine;

la N-(3-méthoxyphényl)-4-(3-méthyl-2-thiényl)-2-pyrimidinamine.

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